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(54) **DERIVATIVES OF INDOLE FOR THE TREATMENT OF CANCER, VIRAL INFECTIONS AND LUNG DISEASES**

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C07D 405/14	(2006.01)
C07D 401/06	(2006.01)
C07F 9/572	(2006.01)
C07F 9/09	(2006.01)
C07F 9/40	(2006.01)
A61K 31/404	(2006.01)
A61K 31/4439	(2006.01)
A61K 31/444	(2006.01)
A61K 31/496	(2006.01)
A61K 31/675	(2006.01)
A61K 31/683	(2006.01)
A61K 45/06	(2006.01)

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CPC ***C07D 209/18*** (2013.01); ***A61K 31/404*** (2013.01); ***A61K 31/444*** (2013.01); ***A61K 31/4439*** (2013.01); ***A61K 31/496*** (2013.01); ***A61K 31/675*** (2013.01); ***A61K 31/683*** (2013.01); ***A61K 45/06*** (2013.01); ***C07D 401/06*** (2013.01); ***C07D 401/14*** (2013.01); ***C07D 405/14*** (2013.01); ***C07F 9/09*** (2013.01); ***C07F 9/40*** (2013.01); ***C07F 9/5728*** (2013.01)

(58) **Field of Classification Search**
CPC C07D 209/18; C07F 9/5728
USPC 548/113, 505; 514/80, 415, 418
See application file for complete search history.

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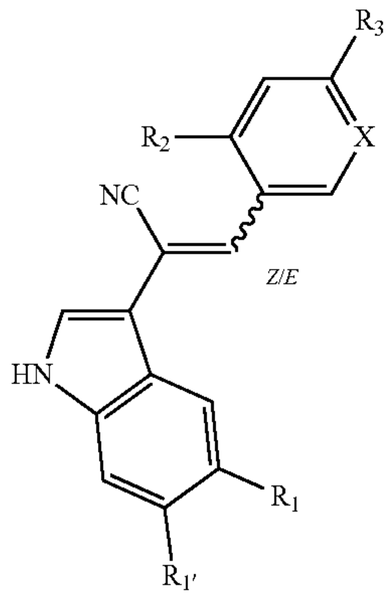
(57) **ABSTRACT**

The present invention relates to a new class of indole derivatives, having a particular MKlp2 inhibition profile and useful as a therapeutic agent, in particular for the treatment of cancer, viral infections and lung diseases.

(I)



12 Claims, 2 Drawing Sheets

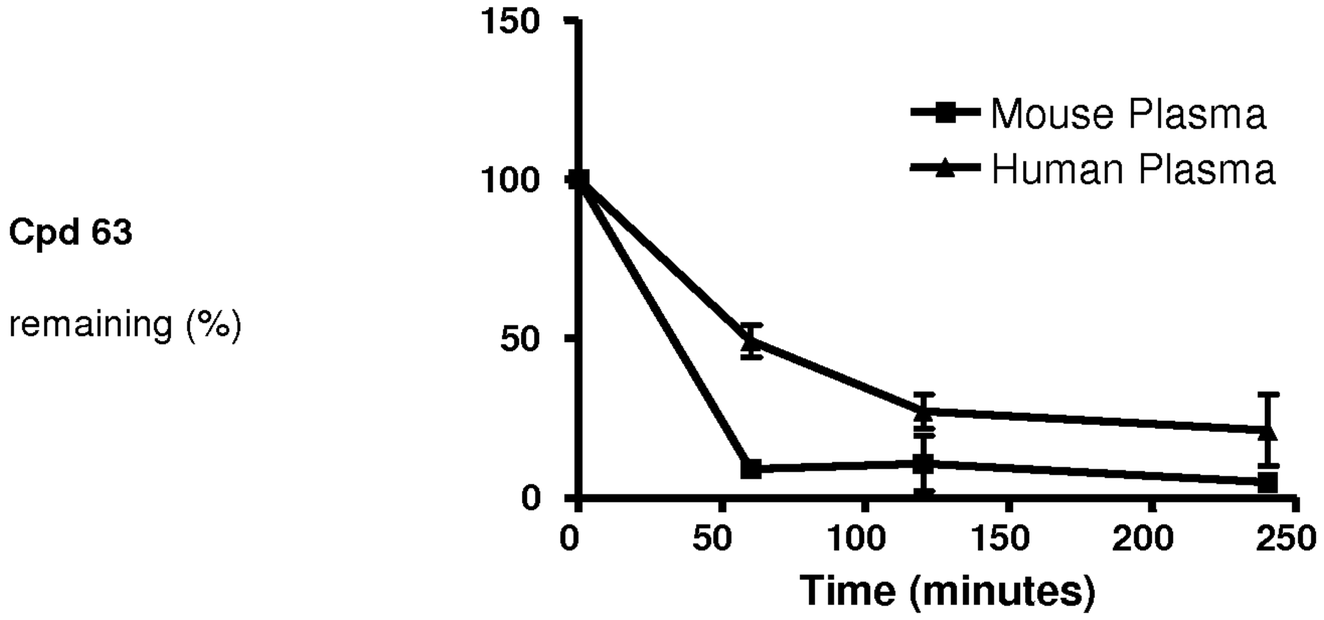


Figure 1

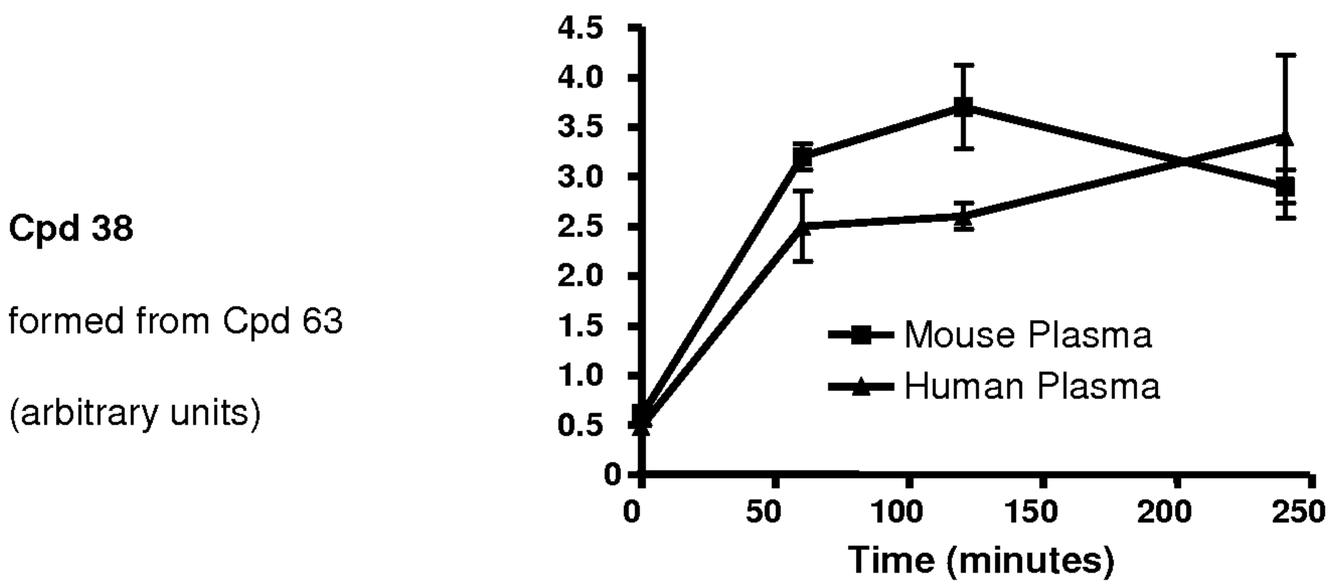


Figure 2

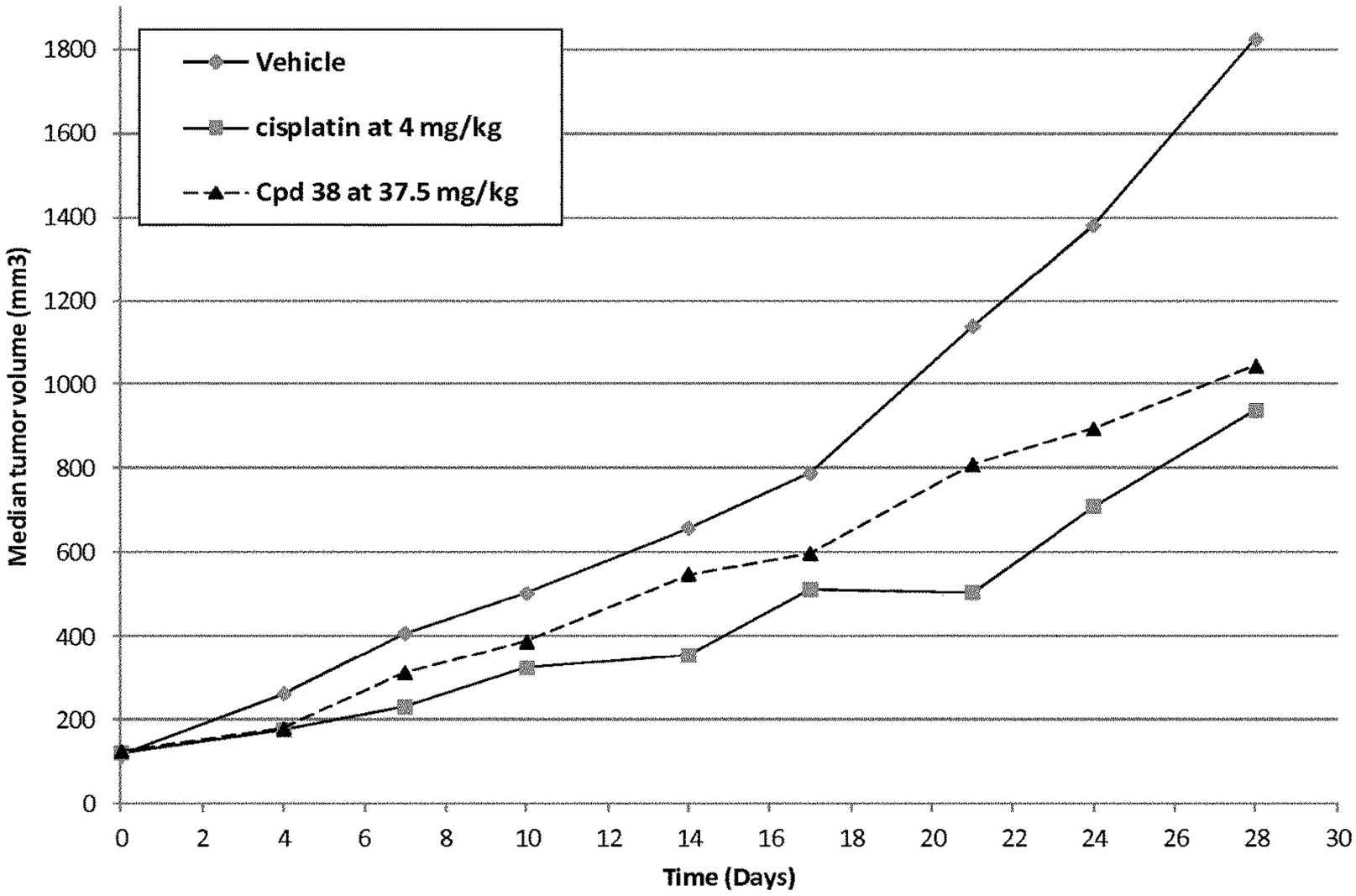


Figure 3

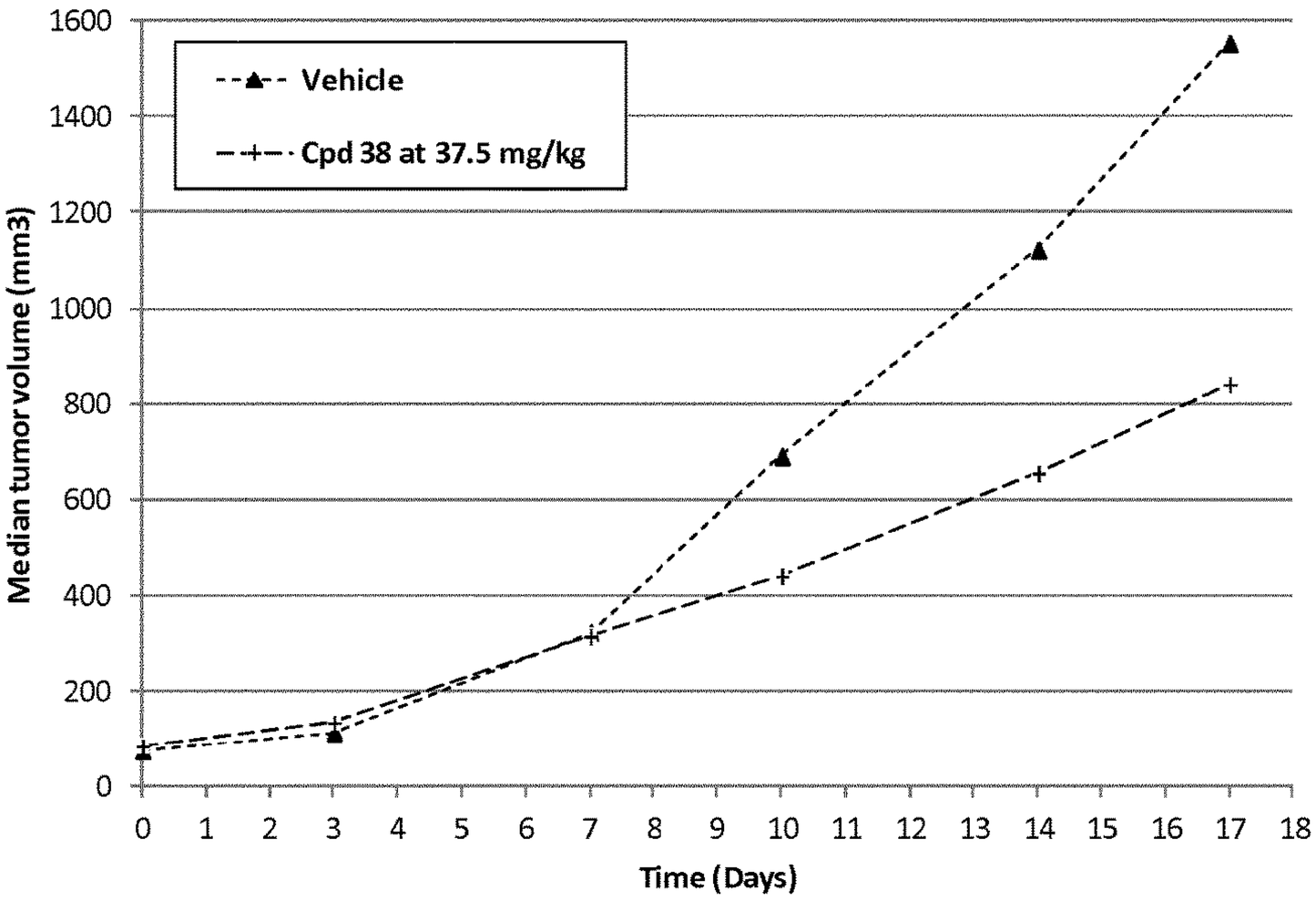


Figure 4

DERIVATIVES OF INDOLE FOR THE TREATMENT OF CANCER, VIRAL INFECTIONS AND LUNG DISEASES

FIELD OF THE INVENTION

The present invention relates to derivatives of indoles and to their application as therapeutics, and in particular to treat the cancer.

BACKGROUND OF THE INVENTION

Cell division is a highly dynamic process, which depends on the proper interaction of mitotic spindle microtubules (MTs) with chromosomes during mitosis. Because of the dynamic nature of mitosis, proteins involved in the process are prime targets for the development of inhibitors that can be used as antimitotic agents with a potential chemotherapeutic value.

Currently, many anti-cancer drugs used in cancer chemotherapy are antimitotic agents, such as taxanes (Paclitaxel, Docetaxel) which target tubulin, the basic component for the polymerization of mitotic microtubules and/or vinca-alkaloids, such as vinorelbine or vinblastine.

Other anti-cancer drugs are alkylating agents, such as cis-platine, DNA intercaling agents, such as doxorubicin, Topoisomerase I or II inhibitors, such as respectively camptothecin and etoposide, and RNA/DNA antimetabolites, such as 5-fluorouracil.

In addition to inhibitors aiming at MT assembly/dynamics and inhibitors targeting mitotic kinases, a new class of targets has emerged, that of kinesin based motor proteins.

Kinesins are proteins which use the free energy of ATP hydrolysis to drive intracellular movement and influence cytoskeleton organization (R. D. Vale and R. J. Fletterick, Annu. Rev. Cell. Dev. Biol. 13, 745-777 (1997)). More than 90 members of this family are known. In particular, a RNAi screen in human cells has identified at least 12 different members of such kinesin superfamily as being actively involved in cell division.

Several members of the kinesin superfamily play thus key roles in mitosis and some of them, such as MKlp2 (also known as KIF20A/RAB6KIFL/Rabkinesin-6, protein number NP_005724), are essential for cytokinesis and more particularly for the implementation of the cleavage furrow and spindle midzone formation. Cytokinesis marks the final step of mitosis and the cell cycle, leading to the production of two daughter cells endowed with a complete set of chromosomes and cytoplasmic organelles.

Many steps of cytokinesis, from cleavage furrow and spindle midzone formation, to transport of proteins to the cell division plane as well as furrow ingression are thought to be dependent on the function of different members of the kinesin superfamily, including Mitotic-Kinesin-Like-Protein-1 (MKlp1) and -2 (MKlp2), M-Phase-Phosphoprotein-1 (MPP1), human KIF4A (and its very close, with 99% identity, homologue KIF4B, both kinesin-4 family) and KIF14. Another protein is Eg5 (also known as KSP) which drives the movement of microtubules in vitro.

Inhibitors of kinesins have already been reported (R. Sakowicz et al., Science 280, 292-295 (1998)) or disclosed, notably in U.S. Pat. No. 6,489,134 and U.S. Pat. No. 6,890,933 but such inhibitors do not show a potential efficacy against MKlp2.

MKlp2 has been shown to be essential for normal cleavage furrow ingression and cytokinesis. Depletion of MKlp2 by siRNA leads to binucleated cells (K Taniuchi et al. Cancer Research 65, 105-112 (2005)). MKlp2 has also been identified as a cytoskeleton-associated proteins essential for lysosomal stability and survival of human cancer cells (L. Groth-Pedersen et al. PLoS One. 7(10), e45381 (2012)). Accordingly, it can thus constitute new target for the development of novel therapeutic strategies against cancer or diseases linked to uncontrolled and/or abnormal cell growth.

Currently, there is a lack of potent inhibitors for this member of the kinesin family that could be used as an anti-cancer agent and for which the specificity of the anti-MKlp2 activity could be sufficient to prevent off target toxicity.

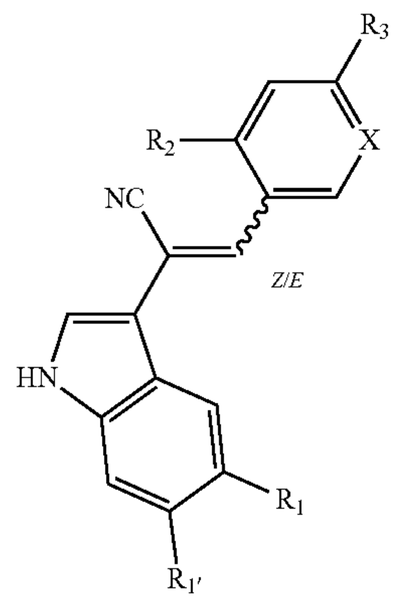
The use of kinesin inhibitors in HIV infection treatment has also been reported in patent application EP 2 455 456. In addition, mitotic kinesin inhibitors are also used for treating lung disease, particularly pulmonary arterial hypertension, such as described in patent application WO 2012/009097.

The inventors have demonstrated that some derivatives of indole are selective inhibitors for MKlp2 in the publication S. Tcherniuk et al. (Angew. Chem. Int. 49, 8228-8231 (2010)) and in the patent application WO 2010/150211. However, alternative or improved inhibitors are still very useful and necessary. A new generation of inhibitors of cytokinesis may in particular be used for the treatment of cancer.

SUMMARY OF THE INVENTION

The present invention relates to compounds of formula (I):

(I)



wherein:

X represents a nitrogen atom, a C—CN unit or a $N^+—O^-$ unit, preferably a nitrogen atom or a C—CN unit;

R_1 and R_1' are such that one is H and the other represents a halogen or a $(C_1$-$C_6)$alkoxy group, optionally substituted by a carboxylic group or one $—NR_{11}R_{12}$ unit wherein R_{11} and R_{12} represent H or a $(C_1$-$C_6)$alkyl group or R_{11} and R_{12} taken together form a 3- to 7-membered ring optionally interrupted by one or several heteroatoms, preferably a $(C_1$-$C_3)$alkoxy group;

R_2 represents:

a radical $(C_1$-$C_6)$alkoxy, $(C_3$-$C_6)$cycloalkoxy, aryloxy, heteroaryloxy, $(C_1$-$C_6)$alkyl-aryloxy, $(C_1$-$C_6)$alkyl-heteroaryloxy, said radicals being optionally substituted by at least one halogen, or a radical thio-$(C_1$-$C_6)$alkyl, thio-aryl, thio-heteroaryl, thio-$(C_1$-$C_6)$alkyl-aryl or thio-$(C_1$-$C_6)$-alkyl-heteroaryl, said

radicals being optionally substituted by at least one halogen or by a $(C_1$-$C_6)$alkoxy group,

a —NR_4R_5 unit, a O—$(C_1$-$C_6)$alkyl-NR_4R_5 unit or a S—$(C_1$-$C_6)$alkyl-NR_4R_5 unit wherein R_4 and R_5 represent H, a $(C_1$-$C_6)$alkyl group, or R_4 and R_5 taken together form a 3- to 7-membered ring, optionally interrupted by one or several heteroatoms, with the proviso that at least one among R_4 and R_5 is not H,

a $NHCOR_6$ unit wherein R_6 represents $(C_1$-$C_6)$alkyl group,

an aryl or heteroaryl group optionally substituted by at least one halogen, a trifluoromethyl group, or a $(C_1$-$C_3)$alkoxy group,a halogen,

with the proviso that if R_1 or R_1' is a $(C_1$-$C_3)$alkoxy group, then R_2 is not a halogen; and

R_3 represents a hydrogen, a $(C_1$-$C_3)$alkyl group, a $(C_1$-$C_3)$alkoxy group or a halogen, advantageously a fluorine;

and the produgs thereof, in which the nitrogen atom of the indole core is substituted by a group selected from the group consisting of a COR_7 and a CO_2R_7 group, wherein R_7 represents:

a $(C_1$-$C_6)$alkyl group, optionally substituted by at least a hydroxy group, a $(C_1$-$C_6)$alkyloxy group, a $(C_1$-$C_6)_n$ polyalkyloxy group wherein n is 1<n<6, a phosphate or pyrophosphate group and salts or $(C_1$-$C_3)$alkyl ester thereof, a R_8 group, a —$NHCO_2R_8$ unit, a COR_8 group, or a CO_2R_8 group, wherein R_8 is:

a $(C_1$-$C_6)$alkyl group,

an aryl, a $(C_1$-$C_6)$alkylaryl, a heteroaryl,

a —NR_9R_{10} unit wherein R_9 and R_{10} represent a hydrogen, a $(C_1$-$C_6)$alkyl group, or R_9 and R_{10} taken together form a 3- to 7-membered ring, optionally interrupted by one or several heteroatoms, and optionally the ring being substituted by at least one $(C_1$-$C_6)$alkyl group;

a NH—NR_9R_{10} unit wherein R_9 and R_{10} are such as defined above; or

a saturated heterocycle or a heteroaryl;

or one of its pharmaceutically acceptable salts;

with the proviso that the compound is not (Z)-3-(4-ethoxy-pyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile.

In a particular embodiment, compounds having formula (I) as defined above are (Z)-isomers (formula Ia) or a prodrug thereof as defined above.

In another particular embodiment, compounds having formula (I) as defined above are (E)-isomers (formula Ib) or a prodrug thereof as defined above.

Particularly, the compound has formula (I), (Ia), or (Ib) as defined above with R_1' being H. More particularly, the compound has formula (I), (Ia), or (Ib) as defined above with R_1 being a halogen chosen among a bromine or a chlorine. Alternatively, R_1, is a halogen chosen among a bromine, a chlorine, or a fluorine. In particular, R_1 is H and R_1, is a halogen chosen among a bromine, a chlorine, or a fluorine

Preferably, the compound has formula (I), (Ia), or (Ib) as defined above with R_2 being:

a radical $(C_1$-$C_6)$alkoxy, phenoxy, said radicals being optionally substituted by at least one halogen;

a halogen;

a R_4—N—R_5 unit or a S—$(C_1$-$C_6)$alkyl-NR_4R_5 unit, wherein R_4 and R_5 represent H, a $(C_1$-$C_6)$alkyl group with the proviso that at least one among R_4 and R_5 is not H,

a $NHCOR_6$ unit wherein R_6 represents $(C_1$-$C_6)$alkyl group,

a radical thio-$(C_1$-$C_6)$alkyl, thio-aryl, thio-heteroaryl, thio-$(C_1$-$C_6)$alkyl-aryl, said radicals being optionally substituted by at least one halogen or by a $(C_1$-$C_6)$ alkoxy group;

an aryl group optionally substituted by at least one halogen, or a trifluoromethyl group; or

a heteroaryl group.

More preferably, the compound has formula (I), (Ia), or (Ib) as defined above with R_2 being:

a radical $(C_1$-$C_6)$alkoxy selected from the group consisting of a methoxy group, an ethoxy group and an isopropoxy group, or a phenoxy group, optionally substituted by a fluorine, such as a trifluoromethyl;

a halogen selected from the group consisting of a fluorine and a chlorine,

a R_4—N—R_5 unit or a S—$(C_1$-$C_6)$alkyl-NR_4R_5 unit wherein R_4 and R_5 represent a methyl or an ethyl group:

a $NHCOR_6$ unit wherein R_6 represents a tert-butyl group;

a radical selected in the group consisting of a thio-methyl group, a thio-ethylgroup, a thio-benzyl group, a thio-pyridinyl group and a thio-phenyl group, optionally substituted by at least one fluorine or a trifluoromethyl group;

a phenyl group optionally substituted by at least one bromine or a trifluoromethyl group; or

a heteroaryl group selected from the group consisting of a furan or a triazol.

In a very particular aspect, the compound is selected from the group consisting of:

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(dimethylamino) pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-dimethylamino) pyridine-3-yl)-acrylonitrile, hydrochloride;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(dimethylamino) pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(E)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-phenoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-phenoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-ethoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-isopropoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(methylthio)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(ethylthio)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(3-bromophenyl) pyridin-3-yl)-acrylonitrile;

(Z)-3-(4-(3-bromophenyl)pyridin-3-yl)-2-(5-chloro-1H-indol-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(phenylthio)pyridin-3-yl)-acrylonitrile;

(Z)-3-(4-(benzylthio)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(3,4-dimethoxy) thio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-fluorophenoxy) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(4-fluorophenoxy) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(diethylamino)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-(trifluoromethyl) phenyl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(4-(trifluoromethyl) phenyl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-((4-fluorophenyl) thio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-((4-fluorophenyl) thio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(pyridine-2-ylthio) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(pyridine-2-ylthio) pyridin-3-yl)-acrylonitrile;
(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)-acrylonitrile;
(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-chloro-1H-indol-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(2-(dimethylamino) ethylthio)pyridin-3-yl)-acrylonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(4-fluorophenoxy)benzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(E)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(ethylthio)benzonitrile;
(Z)-2-(6-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-2-(6-fluoro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-2-(6-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(furan-3-yl)pyridine-1-oxide;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxypyridine-1-oxide;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;
(Z)-3-(2-cyano-2-(6-methoxy-1H-indol-3-yl)vinyl)-4-methoxybenzonitrile;
(Z)-2-(1-acetyl-5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-3-(2-(1-acetyl-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-2-(5-bromo-1-pivaloyl-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-3-(2-(5-bromo-1-pivaloyl-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-methyl 3-(5-bromo-3-(1-cyano-2-(4-methoxypyridin-3-yl)vinyl)-1H-indol-1-yl)-3-oxopropanoate;
(Z)-2-(5-bromo-1-(2-(dimethylamino)acetyl)-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile:
(Z)-2-(4-methylpiperazin-1-yl)ethyl 5-bromo-3-(1-cyano-2-(4-methoxypyridin-3-yl)vinyl)-1H-indole-1-carboxylate;
((Z)-3-(2-(5-bromo-1-(2-(dimethylamino)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-tert-butyl 5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indole-1-carboxylate;
(R,Z)-benzyl-4-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-2-(tert-butoxycarbonylamino)-4-oxobutanoate;
(R,Z)-tert-butyl-5-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-2-(tert-butoxycarbonylamino)-5-oxopentanoate;
(R,Z)-benzyl-2-amino-4-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-4-oxobutanoate;
(Z)-3-(2-(5-bromo-1-(2-(4-methylpiperazin-1-yl)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-3-(2-(5-bromo-1-(2-(4-methylpiperazin-1-yl)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(S,Z)-3-(2-(1-(3-aminobutanoyl)-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(Z)-3-(2-(1-(2-aminoacetyl)-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(Z)-3-(2-(5-bromo-1-(2-(piperazin-1-yl)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(Z)-3-(2-(5-bromo-1-(2-(2-(2-methoxyethoxy)ethoxy) acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(S,Z)-3-(2-(1-(2-amino-3-hydroxypropanoyl)-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(Z)-3-(2-(5-bromo-1-(5-oxopyrrolidine-2-carbonyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(R,Z)-3-(2-(5-bromo-1-(2,6-diaminohexanoyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile dihydrochloride;
(Z)-3-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-3-oxopropyl dihydrogen phosphate;

and their pharmaceutically acceptable salts.

More preferably, the compound is selected from the group consisting of:

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(dimethylamino) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-dimethylamino) pyridine-3-yl)-acrylonitrile, hydrochloride;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(dimethylamino) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(E)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-phenoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-phenoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-ethoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-isopropoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(methylthio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(ethylthio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(3-bromophenyl) pyridin-3-yl)-acrylonitrile;
(Z)-3-(4-(3-bromophenyl)pyridin-3-yl)-2-(5-chloro-1H-indol-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(phenylthio)pyridin-3-yl)-acrylonitrile;
(Z)-3-(4-(benzylthio)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(3,4-dimethoxy) thio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-fluorophenoxy) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(4-fluorophenoxy) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(diethylamino)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-(trifluoromethyl) phenyl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(4-(trifluoromethyl) phenyl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-((4-fluorophenyl) thio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-((4-fluorophenyl) thio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(pyridine-2-ylthio) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(pyridine-2-ylthio) pyridin-3-yl)-acrylonitrile;
(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)-acrylonitrile;
(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-chloro-1H-indol-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(2-(dimethylamino) ethylthio)pyridin-3-yl)-acrylonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(4-fluorophenoxy)benzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(E)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(ethylthio)benzonitrile;
(Z)-2-(6-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-2-(6-fluoro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-2-(6-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(furan-3-yl)pyridine-1-oxide;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxypyridine-1-oxide;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;
(Z)-3-(2-cyano-2-(6-methoxy-1H-indol-3-yl)vinyl)-4-methoxybenzonitrile;

and their pharmaceutically acceptable salts.

Even more preferably, the compound is selected from the group consisting of:

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(E)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-ethoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-isopropoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(methylthio)-pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(phenylthio)pyridin-3-yl)-acrylonitrile;
(Z)-3-(4-(benzylthio)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-fluorophenoxy) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(4-fluorophenoxy) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(dimethylamino) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(diethylamino)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-(trifluoromethyl) phenyl)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-((4-fluorophenyl) thio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-((4-fluorophenyl) thio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(pyridine-2-ylthio) pyridin-3-yl)-acrylonitrile;
(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)-acrylonitrile;
(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-chloro-1H-indol-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(E)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;
(Z)-2-(6-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-2-(6-fluoro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-2-(6-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(furan-3-yl)pyridine-1-oxide;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxypyridine-1-oxide;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;

and their pharmaceutically acceptable salts. The present invention also relates to a compound of the formula (I) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile for use as a drug.

The present invention further relates to a pharmaceutical composition comprising as an active ingredient one compound of the formula (I) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile.

Preferably, the pharmaceutical composition of the present invention is for use in the treatment of cancer.

Optionally, the pharmaceutical composition of the present invention further comprises an additional antitumoral drug, preferably selected from the group consisting of an inhibitor of topoisomerases I or II, a DNA alkylating agent, an anti-metabolic agent, a targeted agent such as a kinase inhibitor, and/or a therapeutical antibody designed to mediate cytotoxicity against the cancer cells or to modulate one of their key biological functions.

More preferably, the pharmaceutical composition of the present invention is for use for treating cancer in combination with radiotherapy, hyperthermia, surgery (e.g., tumor resection) and/or other antitumoral therapies or before, simultaneously or after surgery (e.g., tumor resection).

In addition, the present invention relates to a kit comprising (a) a compound of the present invention; and (b) an additional antitumoral drug as a combined preparation for simultaneous, separate or sequential use, in particular in the treatment of cancer.

Advantageously, the pharmaceutical composition of the present invention is for use in the treatment of viral infections, particularly, HIV infection, HTLV infection or HPV infection.

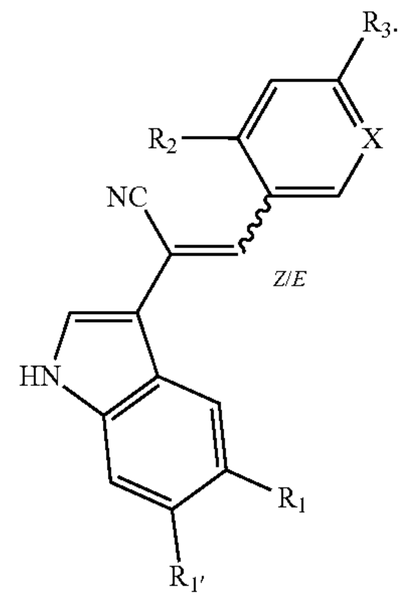
More advantageously, the pharmaceutical composition of the present invention is for use in the treatment of lung diseases, particularly the treatment of pulmonary hypertension.

More advantageously, the pharmaceutical composition of the present invention is for use in the treatment of pathologies associated with dysregulation of MKlp2 or for use in the treatment of pathologies in which the MKlp2 pathway is dysregulated.

The present invention also concerns the use of a compound of the formula (I) as defined above as a research pharmacological tool.

DETAILED DESCRIPTION OF THE INVENTION

The inventors identified a new class of derivatives of indoles of the formula (I):



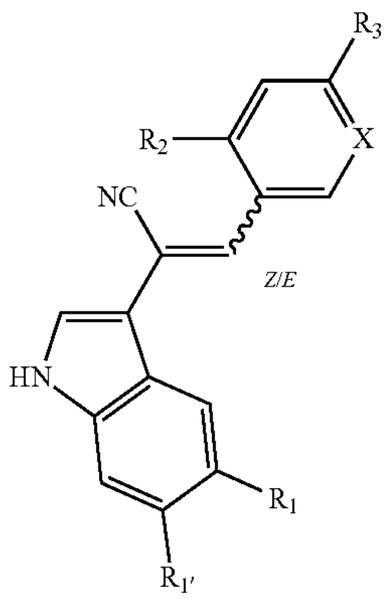
(I)

This new class of compounds presents a therapeutic interest, in particular as effective inhibitors of MKlp2, and consequently, can be used as a drug, for instance for treating cancer, viral infections, lung diseases or pathologies associated with dysregulation of MKlp2 or its pathway.

The inventors, surprisingly, discovered that compounds both substituted in R_1 and R_2 leads to greater MKlp2 inhibition compared to the compounds disclosed in patent application WO 2010/150211.

In particular, a better MKlp2 inhibition profile is surprisingly observed with compounds of the formula (I) of the present invention, wherein R_1 or R_1' represents a (C_1-C_3)-alkoxy group or a halogen while R_2 substituent is present and distinct from a C_1-C_3 alkyl group.

Accordingly, the present invention relates to compound of formula (I):



(I)

wherein:

X represents a nitrogen atom, a C—CN unit or a N^+—O^- unit, preferably a nitrogen atom or a C—CN unit;

R_1 and R_1' are such that one is H and the other represents a halogen or a (C_1-C_6)alkoxy group, optionally substituted by a carboxylic group or one —$NR_{11}R_{12}$ unit wherein R_{11} and R_{12} represent H or a (C_1-C_6)alkyl group or R_{11} and R_{12} taken together form a 3- to 7-membered ring optionally interrupted by one or several heteroatoms;

R_2 represents:

a radical (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryloxy, heteroaryloxy, (C_1-C_6)alkyl-aryloxy, (C_1-C_6)alkyl-heteroaryloxy, said radicals being optionally substituted by at least one halogen,

a hydroxy,

a halogen,

a —NR_4R_5 unit, a O—(C_1-C_6)alkyl-NR_4R_5 unit or a S—(C_1-C_6)alkyl-NR_4R_5 unit wherein R_4 and R_5 represent H or a (C_1-C_6)alkyl group, or R_4 and R_5 taken together form a 3- to 7-membered ring, optionally interrupted by one or several heteroatoms, with the proviso that at least one among R_4 and R_5 is not H,

a $NHCOR_6$ unit wherein R_6 represents (C_1-C_6)alkyl group,

a radical thio-(C_1-C_6)alkyl, thio-aryl, thio-heteroaryl, thio-(C_1-C_6)alkyl-aryl or thio-(C_1-C_6)-alkyl-heteroaryl, said radicals being optionally substituted by at least one halogen or by a (C_1-C_6)alkoxy group,

an aryl group optionally substituted by at least one halogen, a trifluoromethyl group, or a (C_1-C_3)alkoxy group, or

a heteroaryl group, eventually substituted by a halogen, a trifluoromethyl group or a (C_1-C_3)alkoxy group,

with the proviso that if R_1 or R_1' is a (C_1-C_3)alkoxy group, then R_2 is not a halogen; and

R_3 represents a hydrogen, a (C_1-C_3)alkyl group, a (C_1-C_3)alkoxy group or a halogen, advantageously a fluorine;

or one of its pharmaceutically acceptable salts.

In a preferred embodiment, the compound of formula (I) is not (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile. In an alternative embodiment, the compound of formula (I) is such that R_2 is not an ethoxy group.

In a particular embodiment, when R_1 or R_1' is a (C_1-C_6) alkoxy group, optionally substituted by one R_{11}—N—R_{12} unit as above defined or a carboxylic group, then R_2 is not a halogen the compound of formula (I).

In a preferred embodiment, R_1 and R_1' are such that one represents a halogen or a (C_1-C_3)alkoxy group, optionally substituted by a carboxylic group or one R_{11}—N—R_{12} unit as above defined. In a more preferred embodiment, R_1 and R_1' are such that one represents a halogen or a (C_1-C_3)alkoxy group.

The present invention also relates to prodrugs of the compounds disclosed in the present application, preferably prodrugs in which the nitrogen atom of the indole core is substituted. According, the present invention relates to prodrugs in which the nitrogen atom of the indole core is substituted by a group selected from the group consisting of a COR_7 and a CO_2R_7 group, wherein R_7 represents:

a (C_1-C_6)alkyl group, optionally substituted by at least a hydroxy group, a (C_1-C_6)alkyloxy group, a (C_1-C_6). polyalkyloxy group wherein n is 1<n<6, a phosphate or pyrophosphate group and salts or (C_1-C_3)alkyl ester thereof, a R_8 group, a —$NHCO_2R_8$ unit, a COR_8 group, or a CO_2R_8 group, wherein R_8 is:

a (C_1-C_6)alkyl group,

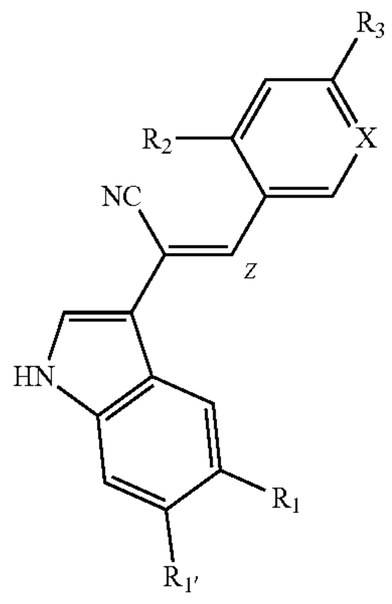
an aryl, a (C_1-C_6)alkylaryl, or a heteroaryl,

a NR_9R_{10} unit wherein R_9 and R_{10} represent a hydrogen, a (C_1-C_6)alkyl group, or R_9 and R_{10} taken together form a 3- to 7-membered ring, optionally interrupted by one or several heteroatoms, and optionally the ring being substituted by at least one (C_1-C_6)alkyl group;

a NH—NR_9R_{10} unit wherein R_9 and R_{10} are such as defined above; or

a saturated heterocycle or a heteroaryl.

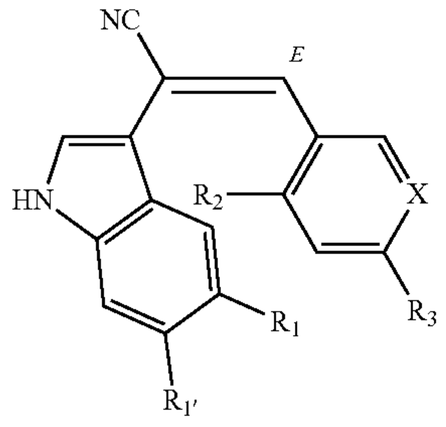
In a particular embodiment, the present invention relates to compounds of formula (Ia):



(Ia)

wherein X, R_1, R_1', R_2, R_3, R_4, R_5 and R_6 are such as defined above. It also relates to prodrugs thereof as defined in the present document.

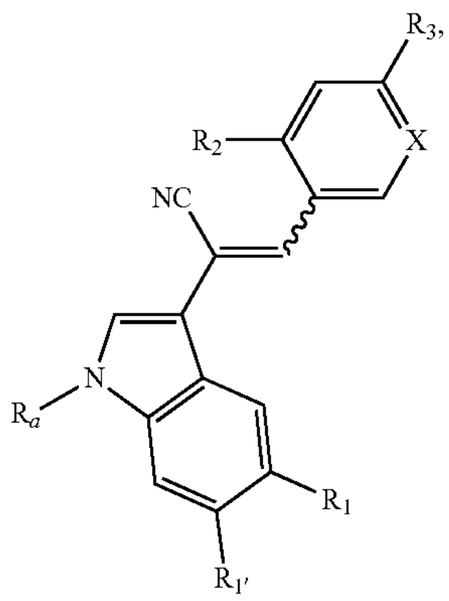
In another particular embodiment, the present invention relates to compounds of formula (Ib):



(Ib)

wherein X, R_1, R_1', R_2, R_3, R_4, R_5 and R_6 are such as defined above. It also relates to prodrugs thereof as defined in the present document.

In another particular embodiment, the present invention relates to compounds of formula (II):



(II)

wherein X, R_1, R_1', R_2, R_3, R_4, R_5 and R_6 are such as defined above, and R_a is a group selected from the group consisting of a COR_S and a CO_2R_7 group, wherein R_7 represents:

- a (C_1-C_6)alkyl group, optionally substituted by at least a hydroxy group, a (C_1-C_6)alkyloxy group, a (C_1-C_6). polyalkyloxy group wherein n is 1<n<6, a phosphate or pyrophosphate group and salts or (C_1-C_3)alkyl ester thereof, a R_8 group, a —$NHCO_2R_8$ unit, a COR_8 group, or a CO_2R_8 group, wherein R_8 is:
  - a (C_1-C_6)alkyl group,
  - an aryl, a (C_1-C_6)alkylaryl, or a heteroaryl,
  - a NR_9R_{10} unit wherein R_9 and R_{10} represent a hydrogen, a (C_1-C_6)alkyl group, or R_9 and R_{10} taken together form a 3- to 7-membered ring, optionally interrupted by one or several heteroatoms, and optionally the ring being substituted by at least one (C_1-C_6)alkyl group;
- a NH—NR_9R_{10} unit wherein R_9 and R_{10} are such as defined above; or
- a saturated heterocycle or a heteroaryl;

or one of its pharmaceutically acceptable salts.

According to the present invention, the terms below have the following meanings:

The terms mentioned herein with prefixes such as for example C_1-C_3 or C_1-C_6 can also be used with lower numbers of carbon atoms such as C_1-C_2 or C_1-C_5. If, for example, the term C_1-C_3 is used, it means that the corresponding hydrocarbon chain may comprise from 1 to 3 carbon atoms, especially 1, 2 or 3 carbon atoms. If, for example, the term C_1-C_6 is used, it means that the corresponding hydrocarbon chain may comprise from 1 to 6 carbon atoms, especially 1, 2, 3, 4, 5 or 6 carbon atoms.

The term "alkyl" refers to a saturated, linear or branched aliphatic group. The term "(C_1-C_3)alkyl" more specifically means methyl (also called "Me"), ethyl (also called "Et"), propyl, or isopropyl, the term "(C_1-C_6)alkyl" more specifically means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl or propyl, pentyl or hexyl.

The term "halogen" corresponds to a fluorine, chlorine, bromine, or iodine atom, preferably a fluorine, chlorine or bromine, and more preferably a chlorine or a bromine.

The term "alkoxy" or "alkyloxy" corresponds to the alkyl group defined hereinabove bonded to the molecule by an —O— (ether) bond. (C_1-C_3)alkoxy includes methoxy, ethoxy, propyloxy, and isopropyloxy. (C_1-C_6)alkoxy includes methoxy, ethoxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, tert-butyloxy, pentyloxy and hexyloxy. The term (C_1-C_6)polyalkyloxy corresponds to n (C_1-C_6) alkyloxy bounded thereby forming a linear poly(C_1-C_6) alkylene glycol chain, preferably a linear polyethylene glycol chain. Preferably, n is 1<n<6.

The term "thio" corresponds to the alkyl group defined hereinabove bounded to the molecule by a —S-(thioether) bound. Thio-(C_1-C_6)alkyl group includes thio-methyl, thio-ethyl, thio-propyl, thio-butyl, thio-pentyl and thio-hexyl.

The term "aryl" is mono- or bi-cyclic aromatic hydrocarbons having from 6 to 12 carbon atoms, optionally substituted. Aryl may be a phenyl (also called "Ph"), biphenyl or naphthyl. In a preferred embodiment, the aryl is a phenyl.

The term "heteroaryl" as used herein corresponds to an aromatic, mono- or poly-cyclic group comprising between 5 and 14 atoms and comprising at least one heteroatom such as nitrogen, oxygen or sulphur atom. Examples of such mono- and poly-cyclic heteroaryl group may be: pyridyl, dihydroypyridyl, thiazolyl, thiophenyl, furanyl, azocinyl, pyranyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxanthinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1-Hindazolyl, purinyl, 4H-quinolizinyl, phtalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, indolinyl, isoindolinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, benzothienyl, benzothiazolyl, isatinyl, dihydropyridyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, thiofuranyl. In a preferred embodiment heteroaryl is an aromatic monocyclic comprising 5 or 6 atoms and comprising at least one heteroatom such as nitrogen, oxygen or sulphur atom. Preferably, heteroaryl is pyridyl, thiazolyl, furanyl, pyranyl, pyrrolyl, imidazolyl, tetrazolyl, benzofuranyl, pyrrolinyl, triazinyl, pyrazinyl, pyridazinyl, triazolyl or tetrazolyl. More preferably, heteroaryl is furanyl or triazolyl.

(C_3-C_6)cycloalkoxy includes cyclopropoxy, cyclobutoxy, cyclopentoxy and cyclohexoxy, (C_3-C_6)cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "saturated heterocycle" as used herein corresponds to a non-aromatic mono- or poly-cyclic group com-

prising between 5 and 14 atoms and comprising at least one heteroatom such as nitrogen, oxygen or sulphur atom. Examples of such heterocycle may be cyclohexanyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, dioxanyl, morpholinyl, piperazinyl. Particularly, the saturated heterocycle may be substituted, for instance by a ketone. More preferably, the saturated heterocycle is oxopyrrolidinyl.

The expression "substituted by at least" means that the radical is substituted by one or several groups of the list.

By "R_x—N—R_y" is intended to refer to a unit "—NR_xR_y".

The terms "carboxylic" "Boc" and "Cbz" respectively correspond to the following groups "—COOH", "—C(=O)—O—$C(CH_3)_3$" and ""—C(=O)—O—CH_2-Phenyl".

The expression "with the proviso that if R_1 or R_1' is a (C_1-C_3)alkoxy group, then R_2 is not a halogen" or "with the proviso that if R_1 or R_1' is a (C_1-C_6)alkoxy group optionally substituted by one R_{11}—N—R_{12} unit as above defined or a carboxylic group, then R_2 is not a halogen" means that, when R_1 or R_1' is a (C_1-C_3)alkoxy group or when R_1 or R_1' is a (C_1-C_6)alkoxy group, optionally substituted by one R_{11}—N—R_{12} unit or a carboxylic group, as above defined, R_2 represents:

- a radical (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryloxy, heteroaryloxy, (C_1-C_6)alkyl-aryloxy, (C_1-C_6)alkyl-heteroaryloxy, said radicals being optionally substituted by at least one halogen,
- a R_4—N—R_5 unit, a O—(C_1-C_6)alkyl-NR_4R_5 unit or a S—(C_1-C_6)alkyl-NR_4R_5 unit wherein R_4 and R_5 represent H, or a (C_1-C_6)alkyl group, or R_4 and R_5 taken together form a 3- to 7-membered ring, optionally interrupted by one or several heteroatoms, with the proviso that at least one among R_4 and R_5 is not H,
- a $NHCOR_6$ unit wherein R_6 represents (C_1-C_6)alkyl group,
- a radical thio-(C_1-C_6)alkyl, thio-aryl, thio-heteroaryl, thio-(C_1-C_6)alkyl-aryl or thio-(C_1-C_6)-alkyl-heteroaryl, said radicals being optionally substituted by at least one halogen or by a (C_1-C_6)alkoxy group,
- an aryl group optionally substituted by at least one halogen, a trifluoromethyl group, or a (C_1-C_3)alkoxy group, or
- a heteroaryl group, eventually substituted by a halogen, a trifluoromethyl group or a (C_1-C_3)alkoxy group.

The pharmaceutically acceptable salts include inorganic as well as organic acids salts. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, maleic, methanesulfonic and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, and in Handbook of Pharmaceutical Salts: Properties, Selection, and Use edited by P. Heinrich Stahl and Camille G. Wermuth 2002. In a preferred embodiment, the salt is selected from the group consisting of maleate, chlorhydrate, bromhydrate, and methanesulfonate.

R_1 and R_1' are such that one is H and the other represents a halogen or a (C_1-C_6)alkoxy group, optionally substituted by one R_{11}—N—R_{12} unit as above defined, or a carboxylic group. Preferably, R_1' or R_1 represents a halogen, typically, a bromine, a chlorine or a fluorine, advantageously a bromine or a chlorine, more specifically a bromine. Alternatively, R_1' or R_1 represent a (C_1-C_6)alkoxy group optionally substituted by one R_{11}—N—R_{12} unit as above defined or a carboxylic group, preferably a (C_1-C_3)alkoxy group optionally substituted by one R_{11}—N—R_{12} unit as above defined or a carboxylic group, more preferably a (C_1-C_3)alkoxy group, advantageously a methoxy, an ethoxy or an isopropoxy, more advantageously a methoxy. R_{11} and R_{12} are such as defined above and preferably represent a (C_1-C_3) alkyl group, and more preferably, a methyl or an ethyl group.

In a preferred embodiment, R_1' is H. In another preferred embodiment, R_1' is a halogen chosen among a bromine, a chlorine, or a fluorine, and R_1 is H.

Particularly, R_2 represents:

- a radical (C_1-C_6)alkoxy or phenoxy, said radicals being optionally substituted by at least one halogen, preferably a bromine, a chlorine or a fluorine, more preferably a fluorine, such as a trifluoromethyl;
- a halogen, preferably a bromine, a chlorine, or a fluorine, more preferably a bromine or a chlorine;
- a R_4—N—R_5 unit or a S—(C_1-C_6)alkyl-NR_4R_5 unit, wherein R_4 and R_5 represent H or a (C_1-C_6)alkyl group, with the proviso that at least one among R_4 and R_5 is not H,
- a $NHCOR_6$ unit wherein R_6 represents (C_1-C_6)alkyl group, advantageously a methyl, an ethyl or a tert-butyl;
- a radical thio-(C_1-C_6)alkyl, thio-aryl, thio-heteroaryl, thio-(C_1-C_6)alkyl-aryl, said radicals being optionally substituted by at least one halogen, a trifluoromethyl, or by a (C_1-C_6)alkoxy group;
- an aryl group optionally substituted by at least one halogen, or a trifluoromethyl group; or
- a heteroaryl group, advantageously a furan, a triazol, a pyridin, a thiazol, a pyran, a pyrrol, an imidazol, a tetrazol, a benzofuran, triazinyl, pyrazinyl, a pyridazin, or a tetrazol.

In a particular embodiment in which R_2 represents a radical (C_1-C_6)alkoxy, the radical (C_1-C_6)alkoxy is selected from the group consisting of a methoxy, propoxy, butoxy, pentoxy and hexoxy.

Preferably, R_2 represents:

- a radical (C_1-C_6)alkoxy selected from the group consisting of a methoxy group, an ethoxy group, and an isopropoxy group, preferably selected from the group consisting of a methoxy group, and an isopropoxy group, or a phenoxy group, optionally substituted by a fluorine, such as a trifluoromethyl;
- a halogen selected from the group consisting of a fluorine and a chlorine,
- a R_4—N—R_5 unit or a S—(C_1-C_6)alkyl-NR_4R_5 unit wherein R_4 and R_5 represent a methyl or an ethyl group:
- a radical selected from the group consisting of a thio-methyl group, a thio-ethyl group, a thio-benzyl group, a thio-pyridinyl group and a thio-phenyl group, optionally substituted by at least one fluorine or a trifluoromethyl group;
- a phenyl group optionally substituted by at least one bromine or a trifluoromethyl group; or
- a heteroaryl group selected from the group consisting of a furan or a triazol.

Particularly, R_3 represents a hydrogen; a (C_1-C_3)alkyl group, preferably a methyl, an ethyl or an isopropyl; a (C_1-C_3)alkoxy group, preferably a methoxy, an ethoxy or an isopropoxy; or a halogene, advantageously a fluorine. Preferably, R_3 is H, methoxy or fluorine. More preferably, R_3 is H.

In a particular embodiment of the invention:

R_1' or R_1 represents a halogen, typically a bromine, a chlorine or a fluorine, advantageously a bromine or a chlorine, more specifically a bromine. In a particular embodiment, R_1' is H. Alternatively R_1' is a halogen chosen among a bromine, a chlorine, or a fluorine, and R_1 is H.

R_2 represents:

- a radical $(C_1\text{-}C_6)$alkoxy, preferably a methoxy, an ethoxy, or an isopropoxy, more preferably a methoxy, or isopropoxy group, and a phenoxy optionally substituted by a fluorine, such as a trifluoromethyl; or
- a halogen, advantageously a fluorine and a chlorine, more advantageously a chlorine; or
- a R_4—N—R_5 unit or a S—$(C_1\text{-}C_6)$alkyl-NR_4R_5 unit wherein R_4 and R_5 represent a $(C_1\text{-}C_6)$alkyl group, preferably a methyl or an ethyl group; or
- a radical thio-$(C_1\text{-}C_6)$alkyl, preferably a thio-methyl or a thio-ethyl; a radical thio-aryl, preferably a thio-phenyl; a radical thio-heteroaryl, preferably, a thio-pyridinyl; or a radical thio-$(C_1\text{-}C_6)$alkyl-aryl, preferably a thio-benzyl; said radicals being optionally substituted by at least a halogen, preferably a fluorine, a trifluoromethyl, or by a $(C_1\text{-}C_6)$alkoxy group, preferably a methoxy, ethoxy, isopropoxy, more preferably a methoxy;
- a phenyl group optionally substituted by at least one halogene, preferably a bromine, or a trifluoromethyl group; or
- a heteroaryl group, preferably a furan, a triazol, a pyridin, a thiazol, a pyran, a pyrrol, an imidazol, a benzofuran, a triazol, or a tetrazol, and more preferably a furan or a triazol; and optionally,

R_3 represents a hydrogen or a $(C_1\text{-}C_3)$alkyl group, preferably a methyl, an ethyl or an isopropyl; a $(C_1\text{-}C_3)$ alkoxy group, preferably a methoxy, an ethoxy or an isopropoxy; or a halogen, advantageously a fluorine. Preferably, R_3 is H, methoxy or fluorine. More preferably, R_3 is H.

In another particular embodiment of the invention

R_1' or R_1 represents a $(C_1\text{-}C_6)$alkoxy group optionally substituted by one R_{11}—N—R_{12} unit as above defined or a carboxylic group, preferably a $(C_1\text{-}C_3)$alkoxy group optionally substituted by one R_{11}—N—R_{12} unit as above defined, preferably wherein R_4 and R_5 represent a $(C_1\text{-}C_3)$alkyl group and more preferably a methyl or an ethyl group, or carboxylic group, more preferably a $(C_1\text{-}C_3)$alkoxy group, still more preferably a methoxy. Advantageously, R_1' is H. Alternatively R_1' is a halogen chosen among a bromine, a chlorine, or a fluorine, and R_1 is H. Optionally, R_1' is a methoxy and R_1 is H.

R_2 represents:

- a radical $(C_1\text{-}C_6)$alkoxy, preferably a methoxy, an ethoxy or an isopropoxy, more preferably a methoxy or an ethoxy, still more preferably a methoxy; or a phenoxy group, optionally substituted by a fluorine, such as a trifluoromethyl; or
- a R_4—N—R_5 unit or a S—$(C_1\text{-}C_6)$alkyl-NR_4R_5 unit wherein R_4 and R_5 represent a $(C_1\text{-}C_6)$alkyl group, preferably a methyl or an ethyl group; or
- a radical thio-$(C_1\text{-}C_6)$alkyl, preferably, a thio-methyl or a thio-ethyl; a radical thio-aryl, preferably a thio-phenyl; a radical thio-heteroaryl, preferably, a thio-pyridinyl; or a radical thio-$(C_1\text{-}C_6)$alkyl-aryl, preferably a thio-benzyl; said radicals being optionally substituted by at least a halogen, preferably a fluorine, a trifluoromethyl, or by a $(C_1\text{-}C_6)$alkoxy group, preferably a methoxy, ethoxy, isopropoxy, more preferably a methoxy;
- a phenyl group optionally substituted by at least one halogene, preferably a bromine, or a trifluoromethyl group; or
- a heteroaryl group, preferably a furan, a triazol, a pyridin, a thiazol, a pyran, a pyrrol, an imidazol, a benzofuran, a pyridazin, or a tetrazol, and more preferably a furan or a triazol; and

R_3 represents a hydrogen or a $(C_1\text{-}C_3)$alkyl group, preferably a methyl, an ethyl or an isopropyl; a $(C_1\text{-}C_3)$ alkoxy group, preferably a methoxy, an ethoxy or an isopropoxy; or a halogen, advantageously a fluorine. More preferably R_3 is H.

The present invention also relates to compounds of formula (II) as above defined.

In a particular embodiment of the invention, R_a is a group selected from the group consisting of a COR_7 and a CO_2R_7 group and R_7 represents a $(C_1\text{-}C_6)$alkyl group, preferably a methyl group or a tert-butyl group.

In another particular embodiment, R_a is a group selected from the group consisting of a COR_7 and a CO_2R_7 group and R_7 is a $(C_1\text{-}C_6)$alkyl group, preferably a methyl, ethyl, propyl group or tert-butyl group, optionally substituted by at least:

- a hydroxy group,
- a $(C_1\text{-}C_6)$.polyalkyloxy group with n=3,
- a R_8 group, a —$NHCO_2R_8$ unit, a COR_8 group, or a CO_2R_8 group wherein R_8 is such as defined above. Preferably, R_8 is:
  - a $(C_1\text{-}C_6)$alkyl group, preferably a methyl or a tert-butyl group,
  - a $(C_1\text{-}C_6)$alkylaryl, preferably, a benzyl group,
  - a NR_9R_{10} unit wherein R_9 and R_{10} preferably represent a hydrogen, a methyl group or R_9 and R_{10} taken together form piperazinyl ring, optionally substituted by a methyl group,
  - a phosphate or pyrophosphate group or a salt thereof, preferably a phosphate group.

In another particular embodiment, R_7 represents:

a NH—NR_9R_{10} unit wherein R_9 and R_{10} are hydrogen, or a saturated heterocycle, preferably oxopyrrolidinyl.

In a preferred embodiment, R_a is a group selected from the group consisting of a COR_7 and a CO_2R_7 group and R_7 represents a methyl or a tert-butyl group, a $(C_1\text{-}C_3)$alkyl substituted by at least one group selected from the group consisting of a CO_2CH_3, $N(CH_3)_2$, piperazinyl-CH_3, NHBoc, Cbz, Boc, NH_2 and phosphate group.

Among the compounds according to the present invention, the following list of compounds may be cited:

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(dimethylamino)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-dimethylamino)pyridine-3-yl)-acrylonitrile, hydrochloride;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(dimethylamino)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(E)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-phenoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-phenoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-ethoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-isopropoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-methylthio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-ethylthio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(3-bromophenyl)pyridin-3-yl)-acrylonitrile;
(Z)-3-(4-(3-bromophenyl)pyridin-3-yl)-2-(5-chloro-1H-indol-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(phenylthio)pyridin-3-yl)-acrylonitrile;
(Z)-3-(4-(benzylthio)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(3,4-dimethoxy)thio) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-fluorophenoxy) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(4-fluorophenoxy) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(diethylamino)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-(trifluoromethyl) phenyl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(4-(trifluoromethyl) phenyl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-((4-fluorophenyl)thio) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-((4-fluorophenyl)thio) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(pyridine-2-ylthio) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(pyridine-2-ylthio) pyridin-3-yl)-acrylonitrile;
(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)-acrylonitrile;
(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-chloro-1H-indol-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(2-(dimethylamino) ethylthio)pyridin-3-yl)-acrylonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(4-fluorophenoxy)benzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(E)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(ethylthio)benzonitrile;
(Z)-N-(3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)pyridin-4-yl)pivalamide;
(Z)-N-(3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)pyridin-4-yl)pivalamide;
(Z)-2-(6-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl) acrylonitrile;
(Z)-2-(6-fluoro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl) acrylonitrile;
(Z)-2-(6-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl) acrylonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(furan-3-yl)pyridine-1-oxide;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxypyridine-1-oxide;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-hydroxypyridin-3-yl) acrylonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-hydroxybenzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;
(Z)-3-(2-cyano-2-(6-methoxy-1H-indol-3-yl)vinyl)-4-methoxybenzonitrile;
(Z)-2-(1-acetyl-5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-3-(2-(1-acetyl-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-2-(5-bromo-1-pivaloyl-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-3-(2-(5-bromo-1-pivaloyl-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(4-methyl 3-(5-bromo-3-(1-cyano-2-(4-methoxypyridin-3-yl)vinyl)-1H-indol-1-yl)-3-oxopropanoate;
(Z)-2-(5-bromo-1-(2-(dimethylamino)acetyl)-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-2-(4-methylpiperazin-1-yl)ethyl 5-bromo-3-(1-cyano-2-(4-methoxypyridin-3-yl)vinyl)-1H-indole-1-carboxylate;
((Z)-3-(2-(5-bromo-1-(2-(dimethylamino)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-tert-butyl 5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indole-1-carboxylate;
(R,Z)-benzyl-4-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-2-(tert-butoxycarbonylamino)-4-oxobutanoate;
(R,Z)-tert-butyl-5-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-2-(tert-butoxycarbonylamino)-5-oxopentanoate;
(R,Z)-benzyl-2-amino-4-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-4-oxobutanoate;
(Z)-3-(2-(5-bromo-1-(2-(4-methylpiperazin-1-yl)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-3-(2-(5-bromo-1-(2-(4-methylpiperazin-1-yl)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(S,Z)-3-(2-(1-(3-aminobutanoyl)-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(Z)-3-(2-(1-(2-aminoacetyl)-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;

(Z)-3-(2-(5-bromo-1-(2-(piperazin-1-yl)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(Z)-3-(2-(5-bromo-1-(2-(2-(2-methoxyethoxy)ethoxy) acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(S,Z)-3-(2-(1-(2-amino-3-hydroxypropanoyl)-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(Z)-3-(2-(5-bromo-1-(5-oxopyrrolidine-2-carbonyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(R,Z)-3-(2-(5-bromo-1-(2,6-diaminohexanoyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile dihydrochloride;
(Z)-3-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl) vinyl)-1H-indol-1-yl)-3-oxopropyl dihydrogen phosphate;
and their pharmaceutically acceptable salts.

Preferably, the following list of compounds may be cited:

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(dimethylamino)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-dimethylamino)pyridine-3-yl)-acrylonitrile, hydrochloride;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(dimethylamino)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(E)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-phenoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-phenoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-ethoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-isopropoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-methylthio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-ethylthio)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(3-bromophenyl)pyridin-3-yl)-acrylonitrile;
(Z)-3-(4-(3-bromophenyl)pyridin-3-yl)-2-(5-chloro-1H-indol-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(phenylthio)pyridin-3-yl)-acrylonitrile;
(Z)-3-(4-(benzylthio)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(3,4-dimethoxy)thio) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-fluorophenoxy) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(4-fluorophenoxy) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(diethylamino)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-(trifluoromethyl) phenyl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(4-(trifluoromethyl) phenyl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-((4-fluorophenyl)thio) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-((4-fluorophenyl)thio) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(pyridine-2-ylthio) pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(pyridine-2-ylthio) pyridin-3-yl)-acrylonitrile;
(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)-acrylonitrile;
(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-chloro-1H-indol-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;
(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(2-(dimethylamino) ethylthio)pyridin-3-yl)-acrylonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(4-fluorophenoxy)benzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(E)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(ethylthio)benzonitrile;
(Z)-N-(3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)pyridin-4-yl)pivalamide;
(Z)-N-(3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)pyridin-4-yl)pivalamide;
(Z)-2-(6-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl) acrylonitrile;
(Z)-2-(6-fluoro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl) acrylonitrile;
(Z)-2-(6-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl) acrylonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(furan-3-yl)pyridine-1-oxide;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxypyridine-1-oxide;
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-hydroxypyridin-3-yl) acrylonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-hydroxybenzonitrile;
(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;
(Z)-3-(2-cyano-2-(6-methoxy-1H-indol-3-yl)vinyl)-4-methoxybenzonitrile;
and their pharmaceutically acceptable salts.

More preferably, the following list of compounds may be cited:

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(E)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-ethoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-isopropoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(methylthio)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(phenylthio)pyridin-3-yl)-acrylonitrile;

(Z)-3-(4-(benzylthio)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-fluorophenoxy) pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(4-fluorophenoxy) pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(dimethylamino)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(diethylamino)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-(trifluoromethyl) phenyl)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-((4-fluorophenyl)thio) pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-((4-fluorophenyl)thio) pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(pyridine-2-ylthio)pyridin-3-yl)-acrylonitrile;

(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)-acrylonitrile;

(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-chloro-1H-indol-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;

(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;

(E)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;

(Z)-2-(6-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl) acrylonitrile;

(Z)-2-(6-fluoro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl) acrylonitrile;

(Z)-2-(6-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl) acrylonitrile;

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(furan-3-yl)pyridine-1-oxide;

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxypyridine-1-oxide;

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;

and their pharmaceutically acceptable salts.

More preferably, the following list of compounds may be cited:

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(E)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(dimethylamino)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(methylthio)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(diethylamino)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;

(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)-acrylonitrile;

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;

(E)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;

(Z)-2-(6-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl) acrylonitrile;

(Z)-2-(6-fluoro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl) acrylonitrile;

(Z)-2-(6-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl) acrylonitrile;

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(furan-3-yl)pyridine-1-oxide;

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxypyridine-1-oxide;

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;

and their pharmaceutically acceptable salts.

In another embodiment, compounds are chosen from the group consisting of:

(Z)-2-(1-acetyl-5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;

(Z)-3-(2-(1-acetyl-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;

(Z)-2-(5-bromo-1-pivaloyl-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;

(Z)-3-(2-(5-bromo-1-pivaloyl-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;

(Z)-methyl 3-(5-bromo-3-(1-cyano-2-(4-methoxypyridin-3-yl)vinyl)-1H-indol-1-yl)-3-oxopropanoate;
(Z)-2-(5-bromo-1-(2-(dimethylamino)acetyl)-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-2-(4-methylpiperazin-1-yl)ethyl 5-bromo-3-(1-cyano-2-(4-methoxypyridin-3-yl)vinyl)-1H-indole-1-carboxylate;
((Z)-3-(2-(5-bromo-1-(2-(dimethylamino)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-tert-butyl 5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indole-1-carboxylate;
(R,Z)-benzyl-4-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-2-(tert-butoxycarbonylamino)-4-oxobutanoate;
(R,Z)-tert-butyl-5-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-2-(tert-butoxycarbonylamino)-5-oxopentanoate;
(R,Z)-benzyl-2-amino-4-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-4-oxobutanoate;
(Z)-3-(2-(5-bromo-1-(2-(4-methylpiperazin-1-yl)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-3-(2-(5-bromo-1-(2-(4-methylpiperazin-1-yl)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(S,Z)-3-(2-(1-(3-aminobutanoyl)-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(Z)-3-(2-(1-(2-aminoacetyl)-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(Z)-3-(2-(5-bromo-1-(2-(piperazin-1-yl)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(Z)-3-(2-(5-bromo-1-(2-(2-(2-methoxyethoxy)ethoxy)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(S,Z)-3-(2-(1-(2-amino-3-hydroxypropanoyl)-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride;
(Z)-3-(2-(5-bromo-1-(5-oxopyrrolidine-2-carbonyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(R,Z)-3-(2-(5-bromo-1-(2,6-diaminohexanoyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile dihydrochloride;
(Z)-3-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-3-oxopropyl dihydrogen phosphate;

and their pharmaceutically acceptable salts.

Preferably, compounds are chosen from the group consisting of:

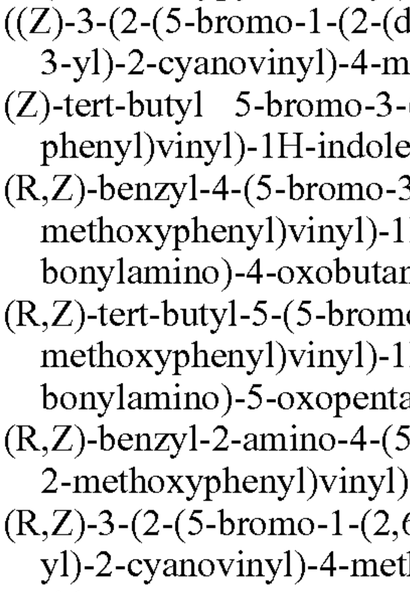
(Z)-2-(1-acetyl-5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-3-(2-(1-acetyl-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-2-(5-bromo-1-pivaloyl-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-3-(2-(5-bromo-1-pivaloyl-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-methyl 3-(5-bromo-3-(1-cyano-2-(4-methoxypyridin-3-yl)vinyl)-1H-indol-1-yl)-3-oxopropanoate;
(Z)-2-(5-bromo-1-(2-(dimethylamino)acetyl)-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile;
(Z)-2-(4-methylpiperazin-1-yl)ethyl 5-bromo-3-(1-cyano-2-(4-methoxypyridin-3-yl)vinyl)-1H-indole-1-carboxylate;
((Z)-3-(2-(5-bromo-1-(2-(dimethylamino)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;
(Z)-tert-butyl 5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indole-1-carboxylate;
(R,Z)-benzyl-4-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-2-(tert-butoxycarbonylamino)-4-oxobutanoate;
(R,Z)-tert-butyl-5-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-2-(tert-butoxycarbonylamino)-5-oxopentanoate;
(R,Z)-benzyl-2-amino-4-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-4-oxobutanoate;
(R,Z)-3-(2-(5-bromo-1-(2,6-diaminohexanoyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile dihydrochloride;
(Z)-3-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-3-oxopropyl dihydrogen phosphate;

and their pharmaceutically acceptable salts.

The chemical structures of some compounds of formula (I) and (II) of the invention are illustrated in the following Tables I and II.

TABLE I

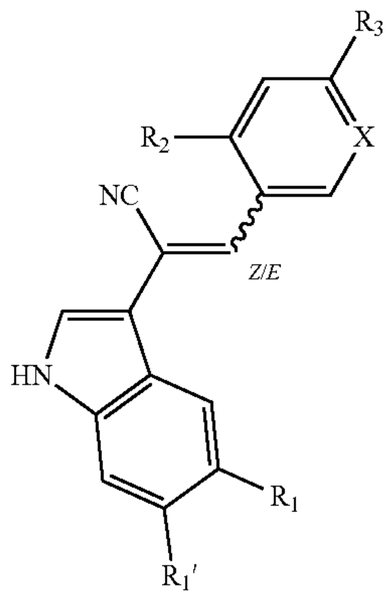
(I)



	X	R1	R1'	R2	R3	Z/E
W02010/150211 Example 1	N	H	H	H	H	Z
W02010/150211 Example 4	N	—O—CH_3	H	H	H	Z
W02010/150211 Example 22	N	—O—CH_2—CH_3	H	H	H	Z

TABLE I-continued

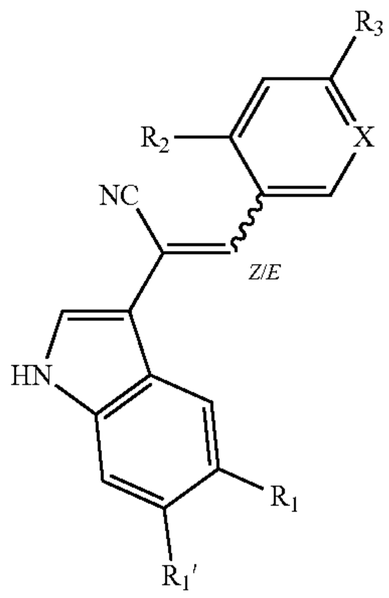
(I)



	X	R1	R1'	R2	R3	Z/E
W02010/150211 Example 23	N	—O—CH—$(CH_3)_2$	H	H	H	Z
W02010/150211 Example 24	N	—Cl	H	H	H	Z
W02010/150211 Example 28	N	—O—CH_3	H	H	—F	Z
W02010/150211 Example 31	N	—O—CH_3	H	—CH_3	H	Z
W02010/150211 Example 47	N	—O—CH_3	H	—Cl	H	Z
W02010/150211 Example 37	N	—Br	H	H	H	Z
W02010/150211 Example 26	N	H	—O—CH_3	H	H	Z
W02010/150211 Example 52	N	—O—CH_3	H	H	—O—CH_3	Z
W02010/150211 Example 30	C—CN	—O—CH_3	H	H	H	Z
Example 2	N	—O—CH_3	H	—O—CH_2—CH_3	H	Z
Example 3	N	—Cl	H	—Cl	H	Z
Example 4	N	—Br	H	—Cl	H	Z
Example 5	N	—Br	H	—O—CH_3	H	Z
Example 5b	N	—Br	H	—O—CH_3	H	E
Example 6	N	—Cl	H	—N—$(CH_3)_2$	H	Z
Example 7	N	—Cl	H	—N—$(CH_3)_2$	H	Z
Example 8	N	—Br	H	—N—$(CH3)_2$	H	Z
Example 9	N	—Cl	H	—O—CH_3	H	Z
Example 9b	N	—Cl	H	—O—CH_3	H	E
Example 10	N	—Cl	H	—O—C_6H_5	H	Z
Example 11	N	—Br	H	—O—C_6H_5	H	Z
Example 12	N	—O—CH_3	H	—O—CH_3	H	Z
Example 13	N	—Br	H	—O—CH_2—CH_3	H	Z
Example 14	N	—Br	H	—O—CH—$(CH_3)_2$	H	Z
Example 15	N	—Br	H	—S—CH_3	H	Z
Example 16	N	—Br	H	—S—CH_2—CH_3	H	Z
Example 17	N	—Br	H	—(C_6H_4)-3-Br	H	Z
Example 18	N	—Cl	H	—(C_6H_4)-3-Br	H	Z
Example 19	N	—Br	H	—S—C_6H_5	H	Z
Example 20	N	—Br	H	—S—CH_2—C_6H_5	H	Z
Example 21	N	—Br	H	—S—C_6H_5-3,4—$(OCH_3)_2$	H	Z
Example 22	N	—Br	H	—O—C_6H_5-4-F	H	Z
Example 23	N	—Cl	H	—O—C_6H_5-4-F	H	Z
Example 24	N	—Br	H	—N—$(CH_2CH_3)_2$	H	Z
Example 25	N	—Br	H	—C_6H_5-4-CF_3	H	Z
Example 26	N	—Cl	H	—C_6H_5-4-CF_3	H	Z
Example 27	N	—Cl	H	—S—C_6H_5-4-F	H	Z
Example 28	N	—Br	H	—S—C_6H_5-4-F	H	Z
Example 29	N	—Cl	H	—C_4H_3O	H	Z
Example 30	N	—Cl	H	—S—C_5H_4N	H	Z
Example 31	N	—Br	H	—S—C_5H_4N	H	Z
Example 32	N	—Br	H	—$C_2H_2N_3$	H	Z
Example 33	N	—Cl	H	—$C_2H_2N_3$	H	Z
Example 34	N	—Br	H	—C_4H_3O	H	Z
Example 34b	N	—Br	H	—C_4H_3O	H	E
Example 35	N	—Cl	H	—O—CH_3	H	Z
Example 36	N	—Br	H	—S—$(CH_2)_2$—N—$(CH_3)_2$	H	Z
Example 37	C—CN	—Br	H	—O—C_6H_5-4-F	H	Z

TABLE I-continued

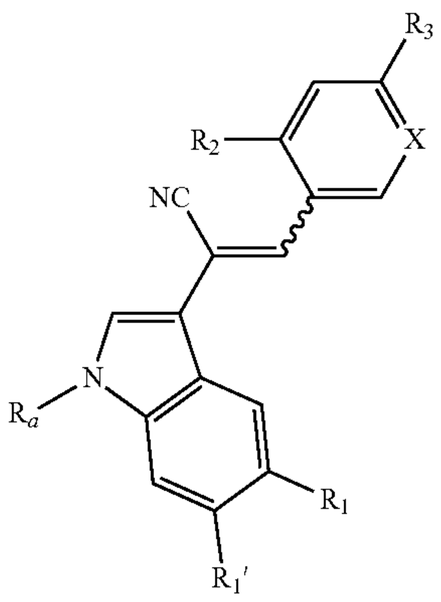
(I)



	X	R1	R1'	R2	R3	Z/E
Example 38	C—CN	—Br	H	—O—CH_3	H	Z
Example 38b	C—CN	—Br	H	—O—CH_3	H	E
Example 39	C—CN	—Br	H	—N—$(CH_3)_2$	H	Z
Example 40	C—CN	—Cl	H	—O—CH_3	H	Z
Example 41	C—CN	—Cl	H	—N—$(CH_3)_2$	H	Z
Example 42	C—CN	—Cl	H	—S—CH_2CH_3	H	Z
Example 43	N	Br	H	—NH—$C(O)C(CH_3)_3$	H	Z
Example 44	N	Cl	H	—NH—$C(O)C(CH_3)_3$	H	Z
Example 45	N	H	—Br	—O—CH_3	H	Z
Example 46	N	H	—F	—O—CH_3	H	Z
Example 47	N	H	—Cl	—O—CH_3	H	Z
Example 48	N^+—O^-	—Br	H	—C_4H_3O	H	Z
Example 49	N^+—O^-	—Cl	H	—O—CH_3	H	Z
Example 50	N	Cl	H	—OH	H	Z
Example 51	C—CN	Br	H	—OH	H	Z
Example 52	C—CN	Cl	H	—OCF_3	H	Z
Example 53	C—CN	Br	H	—OCF_3	H	Z
Example 54	C—CN	H	—O—CH_3	—O—CH_3	H	Z

TABLE II

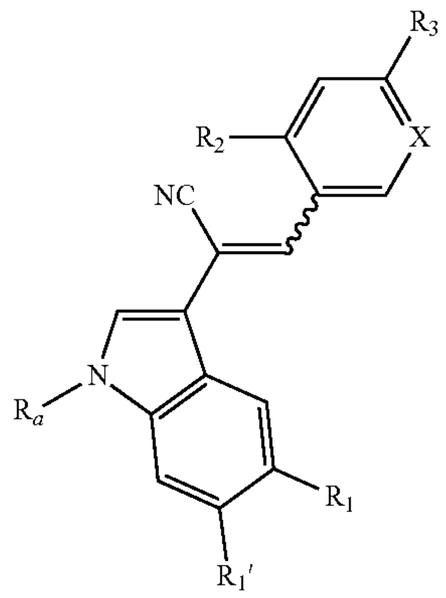
(II)



	X	R1	R1'	R2	R3	Z/E	Ra
Example 55	N	Br	H	OCH_3	H	Z	$COCH_3$
Example 56	C—CN	Br	H	OCH_3	H	Z	$COCH_3$
Example 57	N	Br	H	OCH_3	H	Z	$COC(CH_3)_3$
Example 58	C—CN	Br	H	OCH_3	H	Z	$COC(CH_3)_3$
Example 59	N	Br	H	OCH_3	H	Z	$COCH_2CO_2CH_3$
Example 60	N	Br	H	OCH_3	H	Z	$CONHN(CH_3)_2$
Example 61	N	Br	H	OCH_3	H	Z	$COCH_2N(CH_3)_2$
Example 62	N	Br	H	OCH_3	H	Z	$CO_2(CH_2)_2$-piperazinyl-CH_3
Example 63	C—CN	Br	H	OCH_3	H	Z	$COCH_2N(CH_3)_2$
Example 64	C—CN	Br	H	OCH_3	H	Z	$CO_2C(CH_3)_3$
Example 65	C—CN	Br	H	OCH_3	H	Z	$COCH_2$—CH(NHBoc)Cbz
Example 66	C—CN	Br	H	OCH_3	H	Z	$CO(CH_2)_2$—CH(Boc)—NHBoc
Example 67	C—CN	Br	H	OCH_3	H	Z	$COCH_2$—$CH(NH_2)$—Cbz

TABLE II-continued

(II)



	X	R1	R1'	R2	R3	Z/E	Ra
Example 68	C—CN	Br	H	OCH_3	H	Z	CO—CH_2-piperazinyl-CH_3
Example 69	C—CN	Br	H	OCH_3	H	Z	CO—CH_2-piperazinyl-CH_3•HCl
Example 70	C—CN	Br	H	OCH_3	H	Z	$COCH_2$—$CH(CH_3)NH_2$
Example 71	C—CN	Br	H	OCH_3	H	Z	$COCH_2NH_2$
Example 72	C—CN	Br	H	OCH_3	H	Z	CO—CH_2-piperazinyl
Example 73	C—CN	Br	H	OCH_3	H	Z	$COCH_2O(CH_2)_2O(CH_2)_2OCH_3$
Example 74	C—CN	Br	H	OCH_3	H	Z	$COCH(NH_2)CH_2OH$
Example 75	C—CN	Br	H	OCH_3	H	Z	CO-oxopyrrolidine
Example 76	C—CN	Br	H	OCH_3	H	Z	$COCH(NH_2)$—$(CH_2)_4NH_2$
Example 77	C—CN	Br	H	OCH_3	H	Z	$COCH_2$—$PO(OCH_2CH_3)_2$
Example 78	C—CN	Br	H	OCH_3	H	Z	$COCH_3$—P_2O_7-•$[t\text{-}BuN]_3$+
Example 79	C—CN	Br	H	OCH_3	H	Z	$CO(CH_2)_2PO_4H_2$

The present invention relates to:

a pharmaceutical composition comprising any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments; and/or

a pharmaceutical composition comprising any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments, and a pharmaceutically acceptable carrier; and/or

a pharmaceutical composition comprising (a) any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments, and (b) an additional active ingredient, preferably an additional antitumoral drug; and/or

a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments for use as a drug; and/or

a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments, for use in the treatment of cancer; and/or

a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments, for use in the treatment of viral infections, particularly HIV infection, HTLV infection, or HPV infection; and/or

a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments, for use for the treatment of lung disease, particularly the treatment of pulmonary arterial hypertension; and/or

a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments, for use in the treatment of pathologies associated with dysregulation of MKlp2 or for use in the treatment of pathologies in which the MKlp2 pathway is dysregulated; and/or

a product or kit containing (a) any compound of formula (I), (Ia), (Ib) or (II) as disclosed above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments and (b) an additional active ingredient, preferably an additional antitumoral drug, as a combined preparation for simultaneous, separate or sequential use, in particular in the treatment of cancer; and/or

a combined preparation which comprises (a) any compound of formula (I), (Ia), (Ib) or (II) as disclosed above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments and (b) an additional active ingredient, preferably an additional antitumoral drug, for simultaneous, separate or sequential use, in particular in the treatment of cancer; and/or

a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as

defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments, for the use in the treatment of cancer in combination with radiotherapy, surgery (e.g., tumor resection), hyperthermia and/or other antitumoral therapies or before, simultaneously or after surgery (e.g., tumor resection); and/or

the use of a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments, for the manufacture of a medicament for the treatment of cancer, viral infections, lung diseases and/or pathologies associated with dysregulation of MKlp2 or its pathway, preferably cancer; and/or

the use of a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments and (b) an additional active ingredient, preferably an additional antitumoral drug, for the manufacture of a medicament for the treatment of cancer; and/or

a method for treating a cancer in a subject in need thereof, comprising administering an effective amount of a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments; and/or

a method for treating a cancer in a subject in need thereof, comprising administering an effective amount of a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments and a pharmaceutically acceptable carrier; and/or

a method for treating a cancer in a subject in need thereof, comprising administering an effective amount of a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments, and (b) an additional active ingredient, preferably an additional antitumoral drug; and/or

a method for treating a cancer in a subject in need thereof, comprising administering an effective amount of a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments, and an effective amount of a pharmaceutical composition comprising an additional active ingredient, preferably an additional antitumoral drug; and/or

a method for treating a cancer in a subject in need thereof, comprising administering an effective amount of a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments, in combination with radiotherapy, surgery (e.g., tumor resection), hyperthermia and/or other antitumoral therapies; and/or

a method for treating a viral infection in a subject in need thereof, comprising administering an effective amount of a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments; and/or

a method for treating a lung disease in a subject in need thereof, comprising administering an effective amount of a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments; and/or

a method for treating a pathology associated with dysregulation of MKlp2 or its pathway in a subject in need thereof, comprising administering an effective amount of a pharmaceutical composition as defined above or any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments; and/or

the use of any compound having the formula (I), (Ia), (Ib) or (II) as defined above or (Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)-acrylonitrile including anyone of the disclosed embodiments, as a pharmacological research tool.

The term "cancer", as used herein, refers to the presence of cells possessing characteristics typical of cancer-causing cells, such as uncontrolled proliferation, immortality, metastatic potential, rapid growth and proliferation rate, and certain characteristic morphological features. The cancer may be solid tumor or hematopoietic tumor. Examples of cancer include, for example, leukemia, lymphoma, blastoma, carcinoma and sarcoma. More particular examples of such cancers include chronic myeloid leukemia, acute lymphoblastic leukemia, Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL), squamous cell carcinoma, lung cancer, small-cell lung cancer, non-small cell lung cancer, glioma, gastrointestinal cancer, renal cancer, ovarian cancer, liver cancer, colorectal cancer, endometrial cancer, kidney cancer, prostate cancer, thyroid cancer, neuroblastoma, osteosarcoma, pancreatic cancer, glioblastoma multiforme, cervical cancer, stomach cancer, bladder cancer, hepatoma, breast cancer, oesophagal cancer, colon carcinoma, and head and neck cancer, gastric cancer, germ cell tumor, pediatric sarcoma, sinonasal natural killer, multiple myeloma, acute myelogenous leukemia (AML), chronic lymphocytic leukemia, mastocytosis and any symptom associated with mastocytosis. Preferably, the cancer is a colon cancer, a pancreatic cancer, a breast cancer, a lung cancer and a bladder cancer. More preferably, the cancer is a colon cancer, a pancreatic cancer and a bladder cancer. Optionally, the cancer is associated with a dysregulation of MKlp2 or its pathway. In particular, the cancer is associated with an overexpression of MKlp2.

As used herein, the term "treatment", "treat" or "treating" refers to any act intended to ameliorate the health status of patients such as therapy, prevention, prophylaxis and retardation of the disease. In certain embodiments, such term refers to the amelioration or eradication of a disease or symptoms associated with a disease. In other embodiments, this term refers to minimizing the spread or worsening of the disease resulting from the administration of one or more therapeutic agents to a subject with such a disease.

By "effective amount" it is meant the quantity of the pharmaceutical composition of the invention which pre-

vents, removes or reduces the deleterious effects of the treated disease in mammals, including humans. It is understood that the administered dose may be adapted by those skilled in the art according to the patient, the pathology, the mode of administration, etc. For instance, the compounds of the invention may be used at a dose of 0.01 to 500 mg/kg of body weight/day. In a particular embodiment, the pharmaceutical composition according to the invention comprises 0.01 to 500 mg/kg of the compound of the invention. It is understood that the administered dose may be adapted by those skilled in the art according to the patient, the pathology, the mode of administration, etc.

The administration route can be topical, transdermal, oral, rectal, sublingual, intranasal, intrathecal, intratumoral or parenteral (including subcutaneous, intramuscular, intravenous and/or intradermal). Preferably, the administration route is parental, oral or topical. The pharmaceutical composition is adapted for one or several of the above-mentioned routes. The pharmaceutical composition, kit, product or combined preparation is preferably administered by injection or by intravenous infusion or suitable sterile solutions, or in the form of liquid or solid doses via the alimentary canal.

The pharmaceutical composition can be formulated as solutions in pharmaceutically compatible solvents or as emulsions, suspensions or dispersions in suitable pharmaceutical solvents or vehicles, or as pills, tablets or capsules that contain solid vehicles in a way known in the art. Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and carrier such as cocoa butter, or in the form of an enema. Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredient which is preferably isotonic with the blood of the recipient. Every such formulation can also contain other pharmaceutically compatible and nontoxic auxiliary agents, such as, e.g. stabilizers, antioxidants, binders, dyes, emulsifiers or flavouring substances. The formulations of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefore and optionally other therapeutic ingredients. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof. The pharmaceutical compositions are advantageously applied by injection or intravenous infusion of suitable sterile solutions or as oral dosage by the digestive tract. Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature.

The additional antitumoral drug can be selected in the non-exhaustive list of antitumoral agents consisting of an inhibitor of topoisomerases I or II, an anti-mitotic agent, a DNA alkylating agent, an anti-metabolic agent, a targeted agent such as a kinase inhibitor, and/or a therapeutical antibody designed to mediate cytotoxicity against the cancer cells or to modulate one of their key biological functions.

Anti-mitotic agents include, but are not limited to, paclitaxel, docetaxel and analogs such as larotaxel (also called XRP9881; Sanofi-Aventis), XRP6258 (Sanofi-Aventis), BMS-184476 (Bristol-Meyer-Squibb), BMS-188797 (Bristol-Meyer-Squibb), BMS-275183 (Bristol-Meyer-Squibb), ortataxel (also called IDN 5109, BAY 59-8862 or SB-T-101131; Bristol-Meyer-Squibb), RPR 109881A (Bristol-Meyer-Squibb), RPR 116258 (Bristol-Meyer-Squibb), NBT-287 (TAPESTRY), PG-paclitaxel (also called CT-2103, PPX, paclitaxel poliglumex, paclitaxel polyglutamate or Xyotax™), ABRAXANE® (also called Nab-Paclitaxel; ABRAXIS BIOSCIENCE), Tesetaxel (also called DJ-927), IDN 5390 (INDENA), Taxoprexin (also called docosahexanoic acid-paclitaxel; PROTARGA), DHA-paclitaxel (also called Taxoprexin®), and MAC-321 (WYETH).

Inhibitors of topoisomerases I and/or II include, but are not limited to, etoposide, topotecan, camptothecin, irinotecan, amsacrine, intoplicin, anthracyclines such as doxorubicin, epirubicin, daunorubicin, idarubicin and mitoxantrone. Inhibitors of Topoisomerase I and II include, but are not limited to, intoplicin.

DNA alkylating agent includes, but are not limited to, cisplatin, carboplatin and oxaliplatin. In a preferred embodiment, the DNA alkylating agent is cisplatin.

Anti-metabolic agents block the enzymes responsible for nucleic acid synthesis or become incorporated into DNA, which produces an incorrect genetic code and leads to apoptosis. Non-exhaustive examples thereof include, without limitation, folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors, and more particularly Methotrexate, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, 5-fluorouracil, gemcitabine and capecitabine. The anti-tumoral agent can be alkylating agents including, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas, metal salts and triazenes. Non-exhaustive examples thereof include Uracil mustard, Chlormethine, Cyclophosphamide (CYTOXAN®), Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, cisplatin, carboplatin, oxaliplatin, thiotepa, Streptozocin, Dacarbazine, and Temozolomide.

The anti-tumoral agent can also be a targeted agent, in particular a kinase inhibitor. The kinase may be selected from the group consisting of intracellular tyrosine or serine/threonine kinases, receptors tyrosine or serine/theonine kinase. For instance, the agents may have ability to inhibit angiogenesis based on the inhibitory activities on VEGFR and PDGFR kinases. In particular, the targeted agent can be selected among the multiple kinase inhibitor drugs which are already approved: Gleevec, which inhibits Abl, and Iressa and Tarceva, which both inhibit EGFR, Sorafenib (Nexavar, BAY 43-9006) which inhibits Raf, Dasatinib (BMS-354825) and Nilotinib (AMN-107, Tasigna) which also inhibits Abl, Lapatinib which also inhibits EGFR, Temsirolimus (Torisel, CCI-779) which targets the mTOR pathway, Sunitinib (Stuten, SU11248) which inhibits several targets including VEGFR as well as specific antibodies inactivating kinase receptors: Herceptin and Avastin.

The term "therapy", as used herein, refers to any type of treatment of cancer (i.e., antitumoral therapy), including an adjuvant therapy and a neoadjuvant therapy. Therapy comprises radiotherapy and therapies, preferably systemic therapies such as hormone therapy, chemotherapy, immunotherapy and monoclonal antibody therapy.

The term "adjuvant therapy", as used herein, refers to any type of treatment of cancer given as additional treatment, usually after surgical resection of the primary tumor, in a patient affected with a cancer that is at risk of metastasizing

and/or likely to recur. The aim of such an adjuvant treatment is to improve the prognosis. Adjuvant therapies comprise radiotherapy and therapy, preferably systemic therapy, such as hormone therapy, chemotherapy, immunotherapy and monoclonal antibody therapy.

The term "hormone therapy" or "hormonal therapy" refers to a cancer treatment having for purpose to block, add or remove hormones. For instance, in breast cancer, the female hormones estrogen and progesterone can promote the growth of some breast cancer cells. So in these patients, hormone therapy is given to block estrogen and a non-exhaustive list commonly used drugs includes: Tamoxifen, Toremifene, Anastrozole, Exemestane, Letrozole, Goserelin/Leuprolide, Megestrol acetate, and Fluoxymesterone.

As used herein, the term "chemotherapeutic treatment" or "chemotherapy" refers to a cancer therapeutic treatment using chemical or biological substances, in particular using one or several antineoplastic agents.

The term "radiotherapeutic treatment" or "radiotherapy" is a term commonly used in the art to refer to multiple types of radiation therapy including internal and external radiation therapies or radioimmunotherapy, and the use of various types of radiations including X-rays, gamma rays, alpha particles, beta particles, photons, electrons, neutrons, radioisotopes, and other forms of ionizing radiations.

The term "therapeutical antibody" refers to any antibody having an anti-tumoral effect. Preferably, the therapeutical antibody is a monoclonal antibody. Therapeutic antibodies are generally specific for surface antigens, e.g., membrane antigens. Most preferred therapeutic antibodies are specific for tumor antigens (e.g., molecules specifically expressed by tumor cells), such as CD20, CD52, ErbB2 (or HER2/Neu), CD33, CD22, CD25, MUC-1, CEA, KDR, αVβ3, and the like. The therapeutical antibody include, but is not limited to, antibodies such as trastuzumab (anti-HER2 antibody), rituximab (anti-CD20 antibody), alemtuzumab, gemtuzamab, cetuximab, pertuzumab, epratuzumab, basiliximab, daclizumab, labetuzumab, sevirumab, tuvurimab, palivizumab, infliximab, omalizumab, efalizumab, natalizumab, clenoliximab, and bevacizumab.

The general term "viral infection" defines a condition caused by viruses. The term "HIV infection" more significantly defines a condition caused by the Human Immunodeficiency Virus (HIV), the term "HPV infection" more significantly defines a condition caused by the Human PapillomaVirus (HPV), and the term "HTLV infection" more significantly defines a condition caused by the Human T-cell Lymphotropic Virus (HTLV).

The pulmonary arterial hypertension (PAH) is a syndrome characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular overload and eventually cardiac failure.

Preferably, the pathologies associated with dysregulation of MKlp2 or its pathway are Alzheimer's disease or Creutzfeldt-Jakob's disease.

Finally, the present invention concerns the use of a compound of the formula (I) as defined above as a research pharmacological tool, in particular as MKlp2 inhibitor. It can be used as a laboratory tool or in a screening method.

FIGURES

FIG. **1**: Stability of compound 63 in mouse and human plasma.

FIG. **2**: Amount of formed compound 38 from compound 63 in mouse and human plasma.

FIG. **3**: Evaluation of anti-tumor activity of compound 38 in nude mice bearing subcutaneous human colon HCT-116 xenografts.

FIG. **4**: Evaluation of anti-tumor activity of compound 38 in nude mice bearing subcutaneous non small cell lung carcinoma NCl-H460 xenografts.

EXAMPLES

The following examples illustrate in detail the preparation of compounds of formula (I) according to the invention. The structures of the products obtained have been confirmed by NMR spectra.

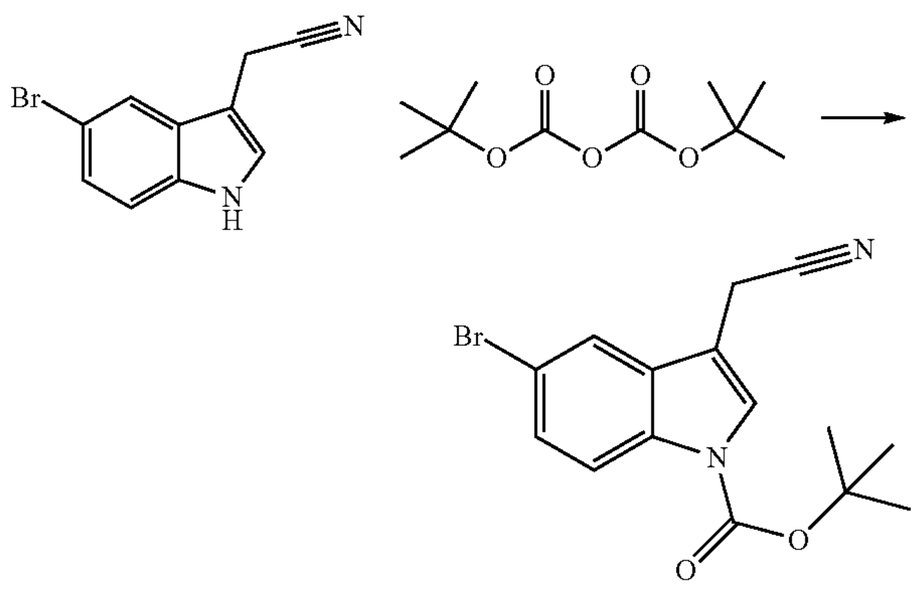
Starting compounds and reactants, unless otherwise indicated, are commercially available or described in literature, or can be prepared according to methods described in literature or known to one skilled in the art.

Example 1

Preparation of Starting Indoles and Aldehydes

A) Syntheses of Starting Indoles

Tert-butyl-5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate



In a 250 mL pear flask, 2-(5-bromo-1H-indol-3-yl)acetonitrile (1.76 g, 7.49 mmol) was dissolved in 70 mL of acetonitrile to give a colorless solution. Di-tert-butyl-dicarbonate (1.922 mL, 8.98 mmol) and DMAP (0.091 g, 0.749 mmol) were added to the solution and the reaction mixture was stirred at RT for 1 h.

TLC: 100% Dichloromethane showed no more starting material.

Then the reaction mixture was poured into 50 mL of water, extracted with 2×50 mL of ethyl acetate and the combined organic layer was successively washed with 1×50 mL of Brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give a yellow oil which crystallized upon standing to give a yellow solid, m=2.59 g (Yield: 99%)

APCI-MS: (M−H)=234

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.00 (d, J=8.8 Hz, 1H), 7.91 (d, J=1.8 Hz, 1H), 7.73 (s, 1H), 7.53 (dd, J=8.8, 2.0 Hz, 1H), 4.12 (d, J=0.9 Hz, 2H), 1.61 (s, 9H).

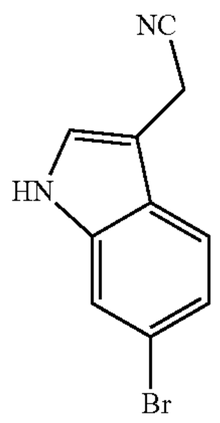
Tert-butyl-5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate is obtained according to the same procedure as for Tert-butyl-5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate.

Tert-butyl
6-X-3-(cyanomethyl)-1H-indole-1-carboxylate

Synthesis of 2-(6-X-1H-indol-3-yl)acetonitrile
(X=bromo, fluoro or chloro)

A mixture of 6-X-1-H-indole-3-carbaldehyde (1 eq), formamide (9 mL/mmol), MeOH (9 mL/mmol) and $NaBH_4$ (3 eq) were stirred 1 h at room temperature. KCN (10 eq) was then added and the resulting mixture was stirred 5 h at 60° C. The reaction was quenched with aqueous NaCl and extracted with $CHCl_3$, dried over Na_2SO_4, filtrated and concentrated. The residue was purified by silicagel chromatography (CH_2Cl_2/MeOH, 100:0 to 90:10) to give the title compound.

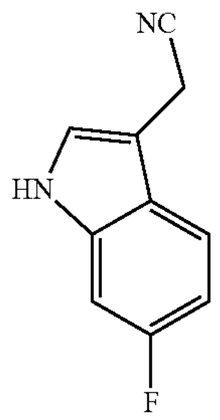
2-(6-bromo-1H-indol-3-yl)acetonitrile



6-bromo-1H-indole-3-carbaldehyde (200.0 mg), formamide (8 mL), $NaBH_4$ (1 01.0 mg), MeOH (8 ml). KCN (580.0 mg). Aspect of the pure product: white solid. (Yield: 67%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 8.21 (s, 1H), 7.59 (s, 1H), 7.48 (d, 1H), 7.31 (d, 1H), 7.24 (s, 1H), 3.84 (s, 1H).

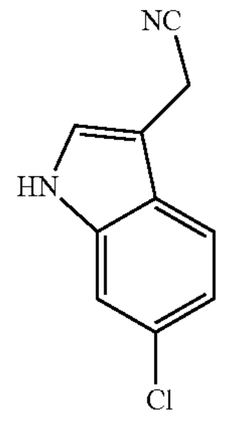
2-(6-fluoro-1H-indol-3-yl)acetonitrile



6-fluoro-1H-indole-3-carbaldehyde (200.0 mg), formamide (10 mL), $NaBH_4$ (138.0 mg), MeOH (10 ml). KCN (791.0 mg). Aspect of the pure product: white solid. (Yield: 75%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: ppm: 8.48 (s, 1H), 7.53-7.50 (m, 1H), 7.14 (s, 1H), 7.09 (d, 1H), 7.0-6.96 (m, 1H), 3.80 (s, 2H).

2-(6-chloro-1H-indol-3-yl)acetonitrile



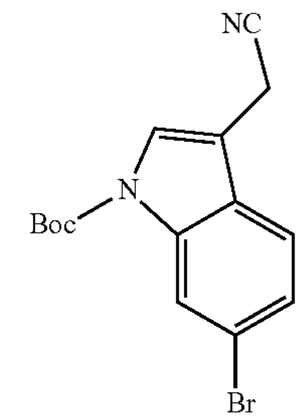
6-chloro-1H-indole-3-carbaldehyde (200.0 mg), formamide (10 mL), $NaBH_4$ (126.0 mg), MeOH (10 ml). KCN (722.0 mg). Aspect of the pure product: white solid. (Yield: 81%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 8.34 (s, 1H), 7.50 (d, 1H), 7.38 (s, 1H), 7.24-7.16 (m, 1H), 7.14 (d, 1H), 3.82 (s, 2H).

Synthesis of Tert-butyl
6-X-3-(cyanomethyl)-1H-indole-1-carboxylate

To a solution of 2-(6-X-1H-indol-3-yl)acetonitrile in CH_2Cl_2, was added Boc_2O (eq) and DMAP (eq). The resulting mixture was stirred 12 h at room temperature, then diluted with CH_2Cl_2, washed with water and concentrated to give the title compound.

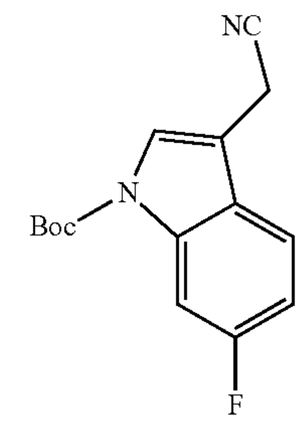
Tert-butyl
6-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate



2-(6-bromo-1H-indol-3-yl)acetonitrile (138.0 mg), DMAP (3.0 mg), Boc_2O (152.0 mg). CH_2Cl_2 (2.8 mL). 12 h at room temperature. Aspect of the pure product: white solid. (Yield: 90%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 8.41 (s, 1H), 7.62 (s, 1H), 7.47-7.36 (m, 2H), 3.78 (s, 2H), 1.70 (s, 9H).

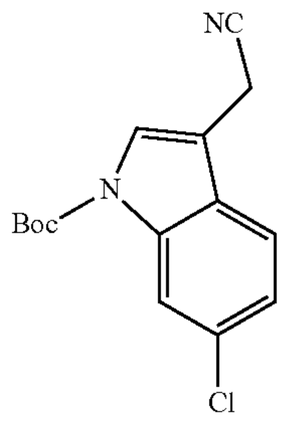
Tert-butyl
6-fluoro-3-(cyanomethyl)-1H-indole-1-carboxylate



2-(6-fluoro-1H-indol-3-yl)acetonitrile (160.0 mg), DMAP (4.3 mg), Boc_2O (238.0 mg). CH_2Cl_2 (4.4 mL). 12 h at room temperature. Aspect of the pure product: white solid. (Yield: 98%).

^1H NMR ($CDCl_3$, 300 MHz) δ ppm: 7.91 (d, 1H), 7.63 (s, 1H), 7.50-7.42 (m, 1H), 7.07 (td, 1H), 3.78 (s, 2H), 1.69 (s, 9H).

Tert-butyl
6-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate

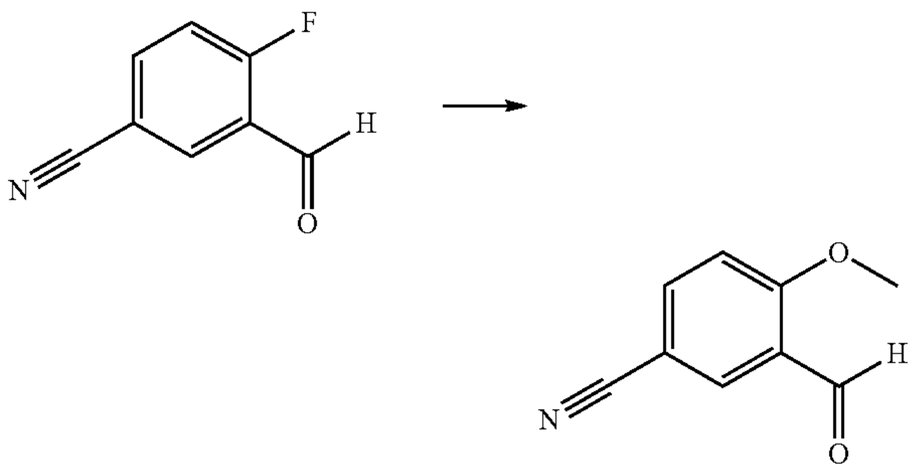


2-(6-chloro-1H-indol-3-yl)acetonitrile (168.0 mg), DMAP (6.0 mg), Boc_2O (233.0 mg). CH_2Cl_2 (4.0 mL). Aspect of the pure product: white solid. (Yield: 86%).

^1H NMR ($CDCl_3$, 300 MHz) δ ppm: 8.25 (s, 1H), 7.64 (s, 1H), 7.45 (d, 1H), 7.29 (d, 1H), 3.77 (s, 2H), 1.70 (s, 9H).

B) Syntheses of Starting Aldehydes

3-formyl-4-methoxybenzonitrile



In a 10 mL reactor flask, 4-fluoro-3-formylbenzonitrile (900 mg, 6.04 mmol) was dissolved under argon in 2 mL of methanol. Sodium methoxide (1.232 mL, 6.64 mmol) was added and the reaction mixture was heated at reflux for 2 h.

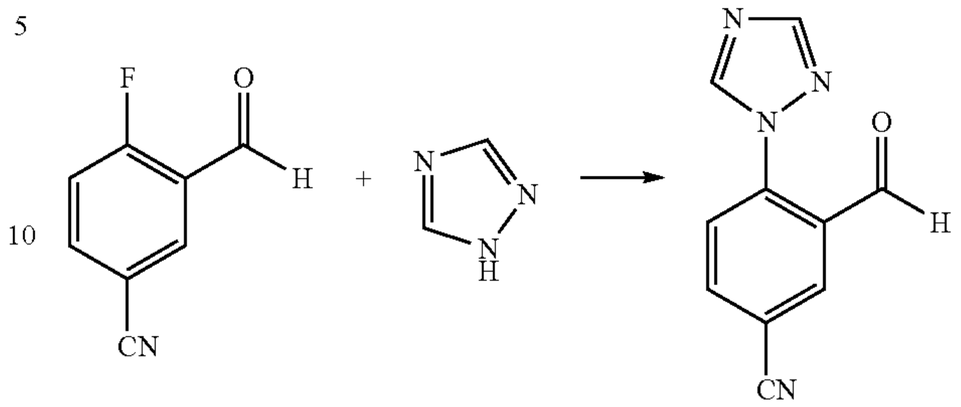
TLC showed no more starting material.

The reaction mixture was poured into 10 mL of water. The resulting solid was filtered, washed with water, DIPE and dried in vacuo. The residue was purified by flash chromatography, eluted with a gradient from petroleum ether to MTBE give 587 mg of a grey solid (Yield: 59%)

LC-MS: 98%

^1H NMR (300 MHz, DMSO-d_6) δ ppm: 10.28 (s, 1H), 8.12 (dd, J=8.8, 2.2 Hz, 1H), 8.05 (d, J=2.1 Hz, 1H), 7.43 (d, J=8.8 Hz, 1H), 4.01 (s, 3H).

3-formyl-4-(1H-1,2,4-triazol-1-yl)benzonitrile



In sealed microwave reactors, 4-fluoro-3-formylbenzonitrile (850 mg, 5.7 mmol) was dissolved in acetonitrile (15 mL), 1H-1,2,4-triazol (590 mg, 8.55 mmol, 1.5 eq) and K_2CO_3 (1575 mg, 11.39 mmol, 2 eq) were added to give a colorless suspension. Then the reaction mixture was stirred and heated at 80° C. for 5 min.

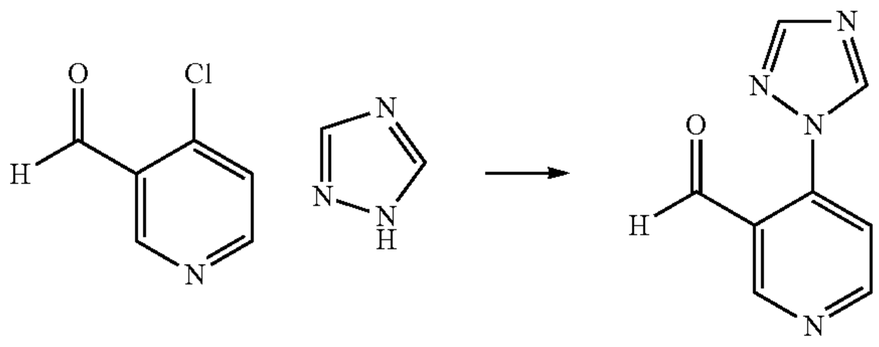
The reaction mixture was poured into 20 mL of water, extracted with 2×20 mL of EtOAc. The combined organic layers were washed with 1×20 mL of water, 1×20 mL of brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give an orange solid, m=983 mg.

The solid was triturated with dichloromethane and petroleum ether, filtered and dried in vacuo at 45° C. overnight to give 493 mg of a brown powder (Yield: 43%)

APCI-MS: $(M+H)^+$=199

^1H NMR (300 MHz, DMSO-d_6) δ ppm: 10.01 (s, 1H), 9.33 (s, 1H), 8.46-8.29 (m, 3H), 8.05 (d, J=9.0 Hz, 1H).

4-(1H-1,2,4-triazol-1-yl)nicotinaldehyde

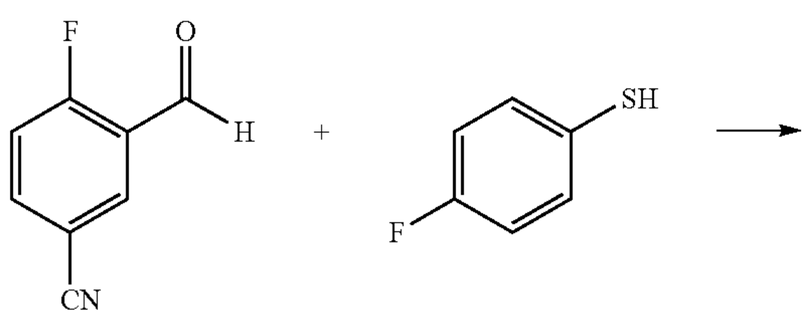


Aspect of the product: yellow solid (Yield: 49%)

APCI-MS: $(M+H)^+$=175

^1H NMR (300 MHz, DMSO-d6) δ ppm: 10.20 (s, 1H), 9.39 (s, 1H), 8.99-8.91 (m, 2H), 8.39 (s, 1H), 7.90 (d, J=5.5 Hz, 1H).

3-formyl-4-(4-fluorophenylthio)benzonitrile



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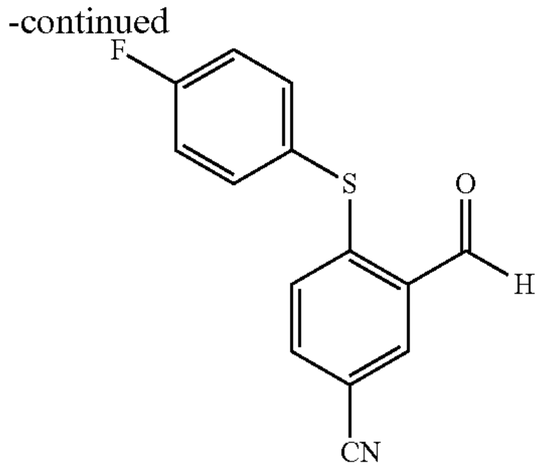


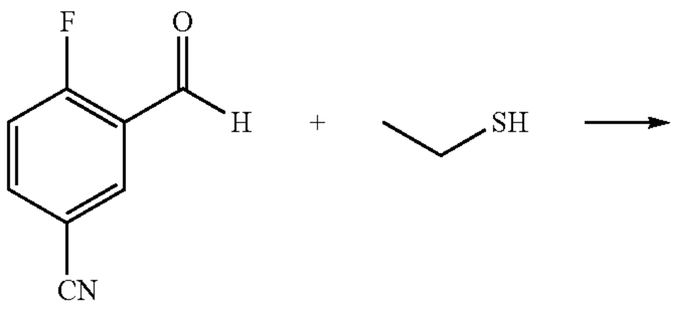
In a 50 mL round-bottomed flask, 4-fluoro-3-formylbenzonitrile (900 mg, 5.73 mmol) and potassium carbonate (872 mg, 6.31 mmol) were suspended in DMF (10 mL) to give a yellow suspension. Then 4-fluorobenzenethiol (0.654 mL, 6.02 mmol) was added and the reaction mixture heated at 70° C. for 18 h. The reaction mixture was poured into water. The solid was filtered, washed with water and with a few amount of DIPE then dried in vacuo to give 1.44 g of a pale yellow solid (Yield: 97%)

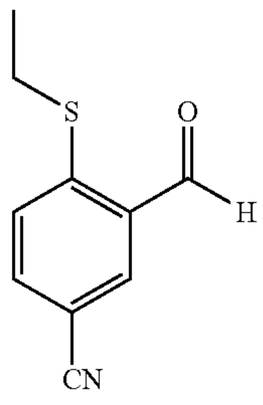
APCI-MS: $(M+H)^+$=257

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.12 (s, 1H), 8.49 (d, J=1.9 Hz, 1H), 7.85 (dd, J=8.5, 2.0 Hz, 1H), 7.71-7.62 (m, 2H), 7.43 (ddd, J=10.9, 6.0, 2.6 Hz, 2H), 6.80 (d, J=8.5 Hz, 1H).

The following examples were prepared according to the previous method.

4-(ethylthio)-3-formylbenzonitrile

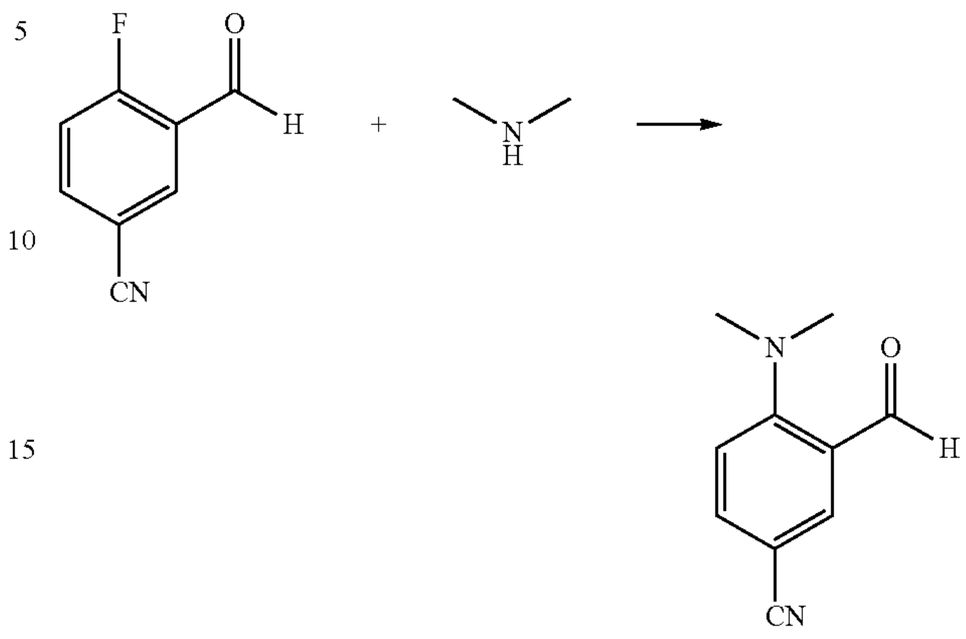




Aspect of the product: yellow solid (Yield: 83%)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.07 (s, 1H), 8.38 (d, J=1.9 Hz, 1H), 7.99 (dd, J=8.4, 1.9 Hz, 1H), 7.63 (d, J=8.5 Hz, 1H), 3.08 (q, J=7.4 Hz, 2H), 1.30 (t, J=7.3 Hz, 3H).

4-(dimethylamino)-3-formylbenzonitrile

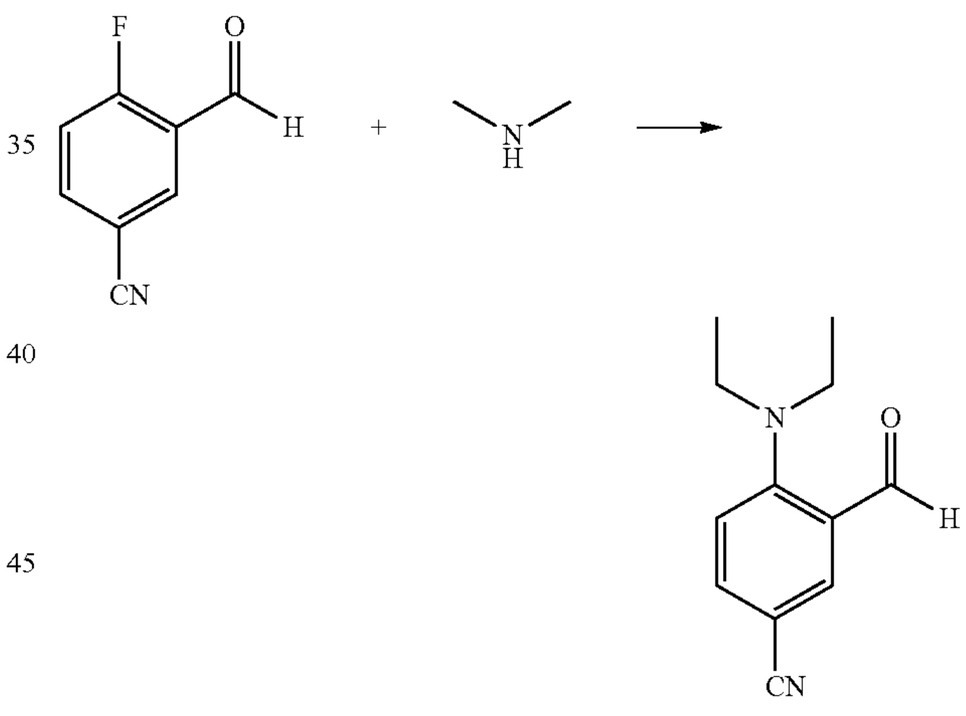


Aspect of the product: orange solid (Yield: 96%)

APCI-MS: $(M+H)^+$=175

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.88 (s, 1H), 8.07 (d, J=2.2 Hz, 1H), 7.72 (dd, J=8.9, 2.2 Hz, 1H), 7.09 (d, J=8.9 Hz, 1H), 2.99 (s, 6H).

4-(diethylamino)-3-formylbenzonitrile

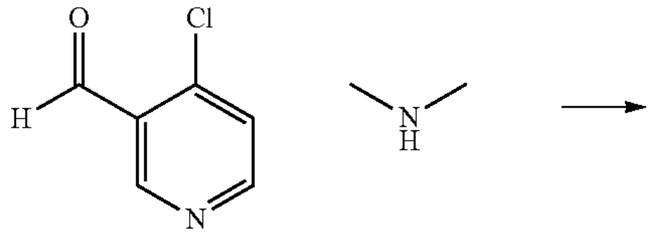


Aspect of the product: yellow solid (Yield: 83%)

APCI-MS: $(M+H)^+$=203

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.91 (s, 1H), 8.00 (d, J=2.2 Hz, 1H), 7.78 (dd, J=8.9, 2.2 Hz, 1H), 7.21 (d, J=8.9 Hz, 1H), 3.44-3.35 (m, 4H), 1.11 (t, J=7.0 Hz, 6H).

4-dimethylamino-3-formyl-pyridine



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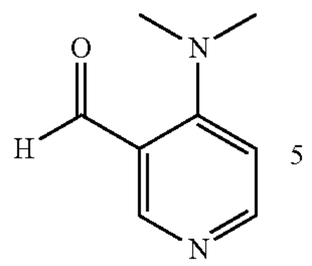


A mixture of 4-chloronicotinaldehyde (500 mg, 3.53 mmol), potassium carbonate (976 mg, 7.06 mmol) and dimethylamine in THF (2.65 mL, 5.30 mmol) was heated at 80° C. for 3 5 hours.

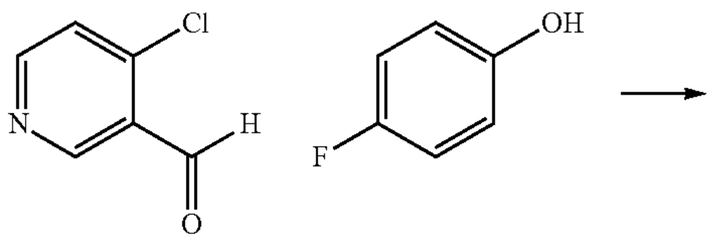
TLC (eluent EtOAc) showed no more starting material.

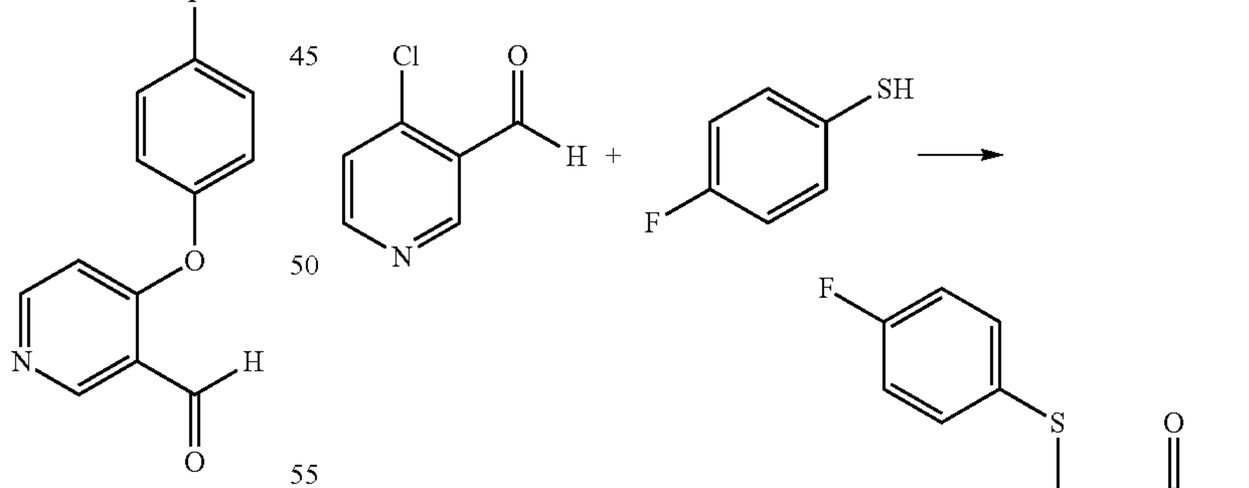
The reaction mixture was concentrated under pressure. Purification by flash chromatography on silica gel column (eluant: CH_2Cl_2/MeOH 90/10) yielded 0.48 g of a pale yellow solid (Yield: 90%)

APCI-MS: $(M+H)^+$=151

^1H NMR (300 MHz, DMSO-d_6) δ ppm: 9.93 (s, 1H), 8.60 (s, 1H), 8.23 (d, J=6.1 Hz, 1H), 6.87 (d, J=6.2 Hz, 1H), 2.99 (s, 6H).

4-fluorophenoxy-3-formylpyridine





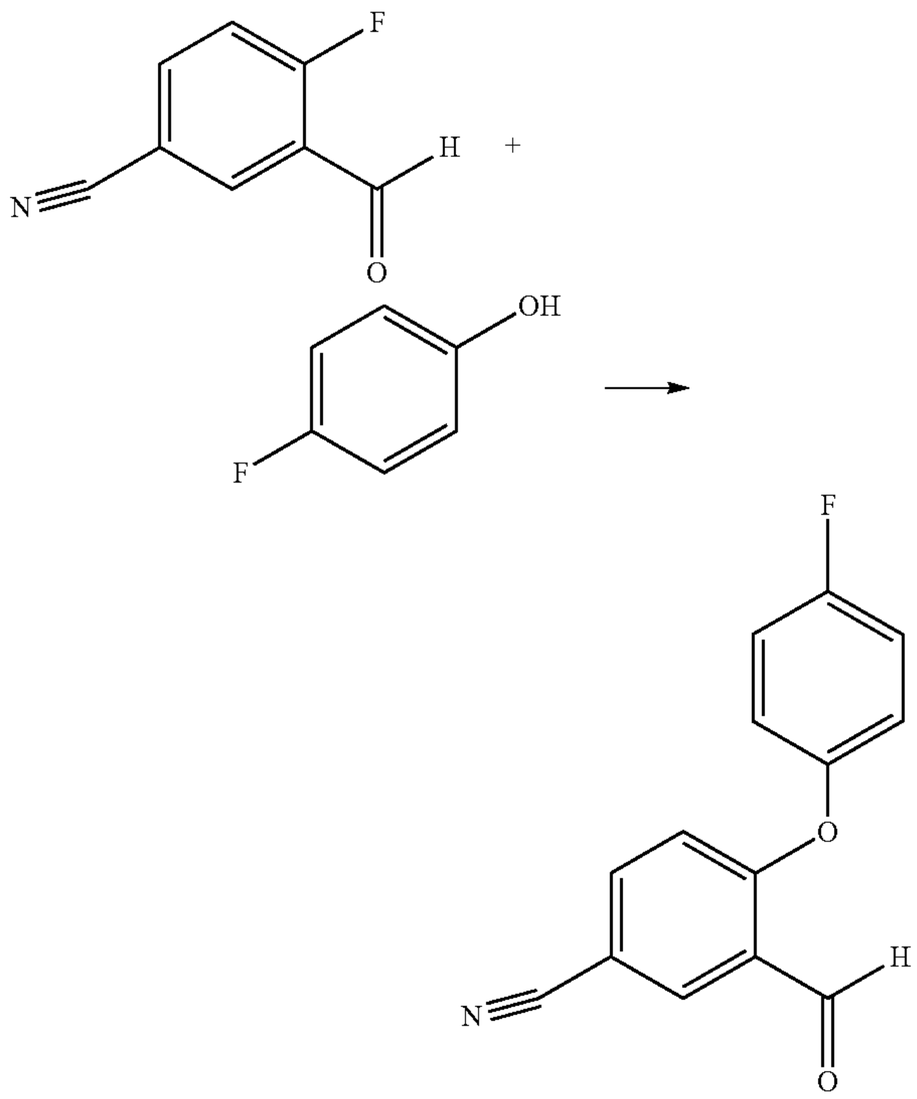
To a solution of 4-fluorophenol (455 mg, 4.06 mmol) in THF [5 mL] was added HNa (162 mg, 4.06 mmol). After stirring for 0.5 hour, 4-chloronicotinaldehyde (500 mg, 3.53 mmol) was added and the reaction mixture was heated at 65° C. for 3 hours.

Then the reaction mixture was diluted with water and brine, extracted with MTBE, dried over $MgSO_4$ and concentrated under reduced pressure to give 617 mg of an oily compound (Yield: 64%)

APCI-MS: $(M+H)^+$=218

The following example was prepared as the previous method.

4-fluorophenoxy-3-formylbenzonitrile



Aspect of the product: yellow solid (Yield: 64%)

APCI-MS: (M−H)=240

^1H NMR (300 MHz, DMSO-d_6) δ ppm: 10.41 (s, 1H), 8.23 (d, J=2.2 Hz, 1H), 8.03 (dd, J=8.8, 2.2 Hz, 1H), 7.40-7.30 (m, 4H), 6.95 (d, J=8.8 Hz, 1H).

4-fluorophenylthio-3-formylpyridine

A mixture of 4-chloronicotinaldehyde (500 mg, 3.53 mmol), potassium carbonate (537 mg, 3.89 mmol) and 4-fluorobenzenethiol (0.403 mL, 3.71 mmol) in DMF (10 mL) was heated at 70° C. for 1 h.

The reaction mixture was quenched with water, extracted with 3×20 mL of AcOEt, the combined organic were washed with brine, dried over Na_2SO_4, filtered and concentrated

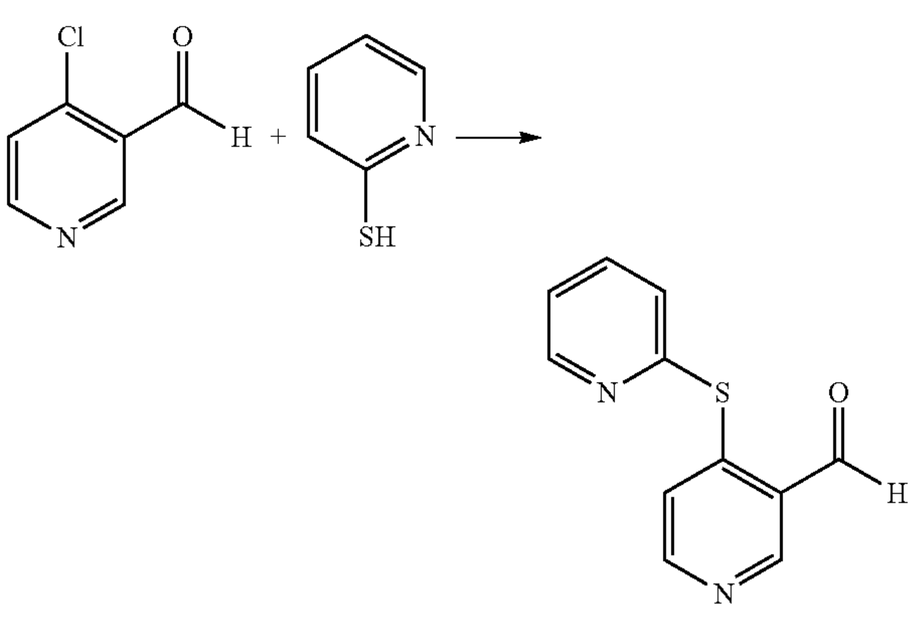
under vacuum to give a brown oil. The oil was triturated with 5 mL of DIPE to give 0.46 g of a beige solid (Yield: 55%).

APCI-MS: $(M+H)^+$=234

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.19 (s, 1H), 9.03 (s, 1H), 8.45 (d, J=5.6 Hz, 1H), 7.69 (dd, J=8.5, 5.5 Hz, 2H), 7.45 (t, J=8.7 Hz, 2H), 6.61 (d, J=5.6 Hz, 1H).

The following examples were prepared as the previous method.

4-(pyridin-2-ylthio)nicotinaldehyde

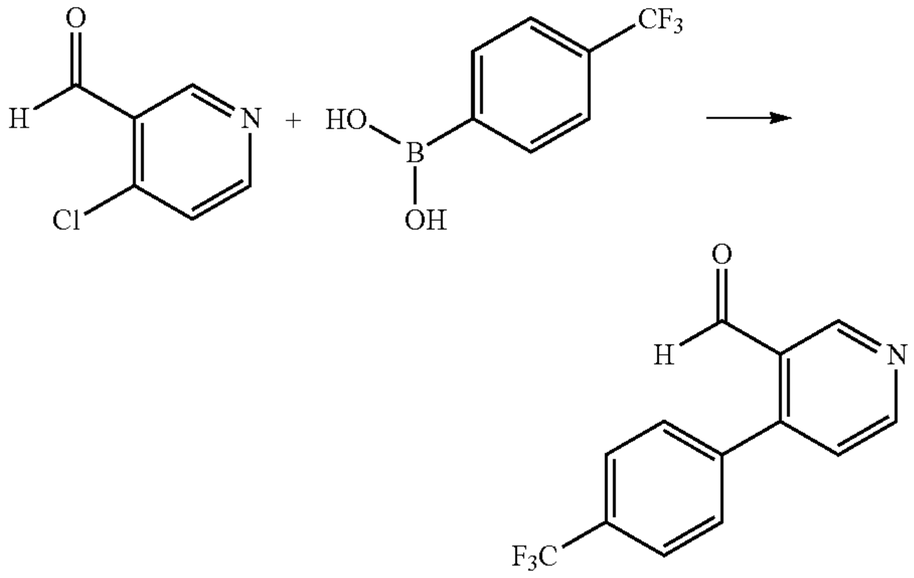


Aspect of the product: yellow solid (Yield: 61%)

APCI-MS: $(M+H)^+$=217

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.18 (s, 1H), 9.04 (s, 1H), 8.68 (d, J=3.7 Hz, 1H), 8.51 (d, J=5.5 Hz, 1H), 7.95 (td, J=7.7, 1.9 Hz, 1H), 7.74 (d, J=7.8 Hz, 1H), 7.51 (dd, J=6.5, 4.8 Hz, 1H), 7.00 (d, J=5.5 Hz, 1H).

3-formyl-4-(4-trifluorophenyl)benzonitrile



In a 50 mL pear flask, magnetic stirrer, 4-chloronicotinaldehyde (500 mg, 3.53 mmol), 4-trifluoromethyl)phenylboronic acid (671 mg, 3.53 mmol), triphenylphosphine (55.6 mg, 0.212 mmol), palladium(II) acetate (47.6 mg, 0.212 mmol) and potassium carbonate (976 mg, 7.06 mmol) were added successively followed by 1,2-dimethoxyethane (10 mL) and water (2.5 mL). The reaction mixture was stirred and heated at 85° C. for 18 hours (LC/MS showed no starting material).

20 mL of water and 20 mL of ethyl acetate were added. The mixture was filtered over Celite and the cake rinsed with 20 mL of ethyl acetate. Organic phases were washed twice with brine, dried over sodium sulfate, filtered and the solvent was removed to give 890 mg of an oil.

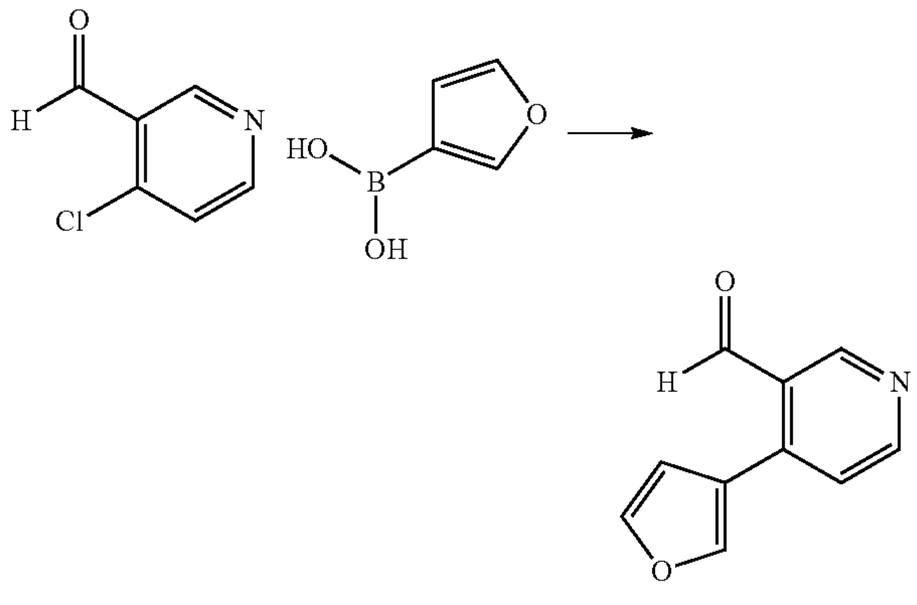
The crude oil was purified by flash chromatography on SiO_2, eluted with 100% dichloromethane then 95/5 dichloromethane/acetone to give 370 mg of a grey solid (Yield: 42%)

APCI-MS: $(M+H)^+$=252

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.00 (s, 1H), 9.08 (s, 1H), 8.90 (d, J=5.1 Hz, 1H), 7.92 (d, J=8.1 Hz, 2H), 7.78 (d, J=8.0 Hz, 2H), 7.61 (dd, J=5.1, 0.6 Hz, 1H)

The following example was prepared as the previous method.

4-(furan-3-yl)nicotinaldehyde



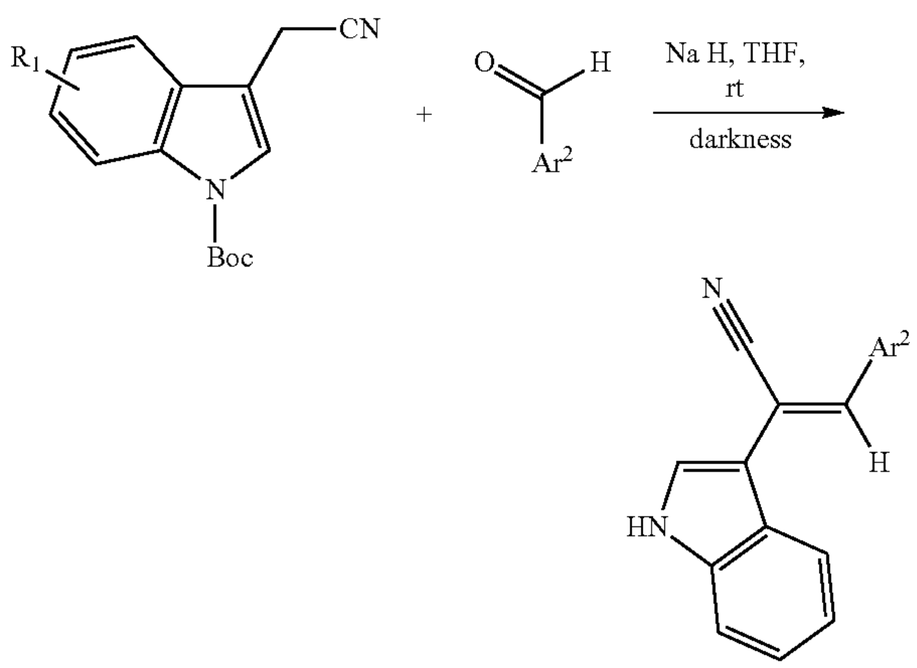
Aspect of the product: yellow solid (Yield: 64%)

LC-MS: $(M+H)^+$=174

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.24 (s, 1H), 8.96 (s, 1H), 8.78 (s, 1H), 8.25 (s, 1H), 7.90 (s, 1H), 7.62 (s, 1H), 6.99 (s, 1H).

Preparation of Examples 2 to 53

Method A: Knoevenagel Condensation



To a solution of cyanomethyl-indole-1-carboxylic acid tert-butyl ester (1 eq.) in THF was added sodium hydride

(1.5 eq.) under an argon atmosphere. The reaction apparatus was protected from light and the mixture stirred at room temperature for 1 hour. Then the reaction mixture was cooled to 0° C. and the aldehyde (1.2 eq.) was added in protions.

The mixture was stirred at room temperature for 24 or 48 hours, then quenched with saturated ammonium chloride aqueous solution and extracted with AcOEt. The combined organic layers were dried over $MgSO_4$ and evaporated under vacuo. When the desired compound protected with a Boc group remained as a side product of the reaction, the reaction mixture was treated with a solution of HCl in dioxane or an aquous solution of NaOH 1N to complete the Boc deprotection. Then the crude residue was triturated with a minimum of solvant (MeOH or CH_2Cl_2 or Et_2O), filterated, washed with Et_2O, and dried in vacuo for 12 hours (in dark) to afford the corresponding acrylonitrile.

Method B: SN_{AR} reactions from (Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile or (Z)-2-(5-Bromo-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile

To a solution of 4-chloropyridine derivative (Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile or (Z)-2-(5-Bromo-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile (1 eq.) in MeOH, EtOH or isopropanol was added KOH (2 to 5 eq.) under an argon atmosphere. The reaction apparatus was protected from light and the mixture was refluxed overnight. The mixture was diluted with AcOEt, washed with water then brine. The organic layer was dried over $MgSO_4$ and reduced in vacuo. The crude product was purified by trituration with AcOEt or by flash chromatography to afford the SN_{AR} derivative.

Method C: SN_{AR} reactions from (Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile or (Z)-2-(5-Bromo-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile

To a solution of 4-chloropyridine derivative -(Z)-2-(5-Bromo-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile (1 eq.) in DMF was added NaSMe or NaSEt (2 eq.) under an argon atmosphere. The reaction apparatus was protected from light and the mixture was stirred overnight at room temperature. The mixture was diluted with AcOEt, washed with water then brine. The organic layer was dried over $MgSO_4$ and reduced in vacuo. The crude product was purified by trituration with AcOEt to afford the SN_{AR} derivative.

Method D: SN_{AR} reactions from (Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile or (Z)-2-(5-Bromo-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile

To a solution of 4-chloropyridine derivative (Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile or (1 eq.) in DMF were added arylthiol (1.1 eq.) and sodium or potassium carbonate (2 eq.) under an argon atmosphere. The reaction apparatus was protected from light and the mixture was stirred overnight at room temperature. The mixture was diluted with AcOEt, washed with water then brine. The organic layer was dried over $MgSO_4$ and reduced in vacuo. The crude product was purified by trituration with AcOEt to afford the SN_{AR} derivative.

Method E: E Isomers

Z isomers were dissolved in ethanol and subjected to a 150 W halogen lamp with a continuous argon flux until there was no more starting material (TLC). The solution was then concentrated and the residue was purified by C18 chromatography to give the title compound.

Method F: Synthesis of (Z)-2-(6-X-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile

To a solution of tert-butyl 6-X-3-(cyanomethyl)-1H-indole-1-carboxylate(1 eq) in THF, was added NaH (eq). The resulting mixture was stirred 10 min at room temperature and 4-methoxynicotinaldehyde (1.3 eq) was added with one drop of DMF. The mixture was stirred at room temperature hidden from light. The reaction was quenched with aqueous NH_4Cl and extracted with AcOEt, dried over Na_2SO_4, filtrated and concentrated. The residue was dissolved with THF and NaOH 2.5 M was added. The system was stirred at room temperature hidden from light, diluted with AcOEt, dried over Na_2SO_4, filtrated and concentrated. The residue was taken off with a minimal amount of AcOEt and filtrated to give the title compound.

Method G: Synthesis of (Z)-3-(2-(5-X-1H-indol-3-yl)-2-cyanovinyl)-4-methoxypyridine 1-oxide

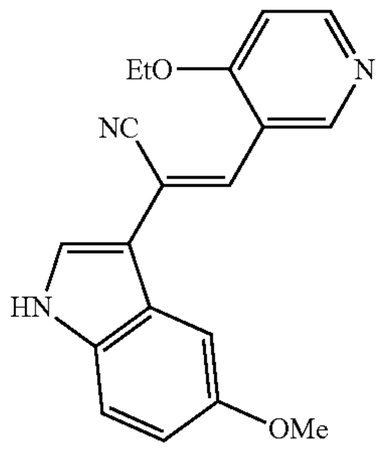
To a solution of (Z)-2-(5-X-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile in THF was added m-CPBA (1 eq), the resulting mixture was stirred 12 h at room temperature, hidden from light and a new portion of m-CPBA (0.5 eq) was added. After additional 4 h of stirring, the mixture was concentrated and the residue was triturated in AcOEt and filtrated to give the title compound.

Method H: Synthesis of (Z)-3-(2-(5-X-1H-indol-3-yl)-2-cyanoyinyl)-4-(trifluoromethoxy)benzonitrile

To a solution of tert-butyl 5-X-3-(cyanomethyl)-1H-indole-1-carboxylate (1 eq) in THF, was added NaH (3 eq). The resulting mixture was stirred 10 min at room temperature and 3-formyl-4-(trifluoromethoxy)benzonitrile (1 eq) was added with one drop of DMF. The mixture was stirred at room temperature hidden from light. The reaction was quenched with aqueous NH_4Cl and extracted with AcOEt, dried over Na_2SO_4, filtrated and concentrated. The residue was dissolved with THF and NaOH 2.5 M was added. The system was stirred at room temperature hidden from light, diluted with AcOEt, dried over Na_2SO_4, filtrated and concentrated. The residue was purified by silicagel chromatography (CH_2Cl_2/MeOH, 100:0 to 90:10) to give the title compound.

Example 2

(Z)-3-(4-ethoxypyridin-3-yl)-2-(5-methoxy-1H-indol-3-yl)acrylonitrile



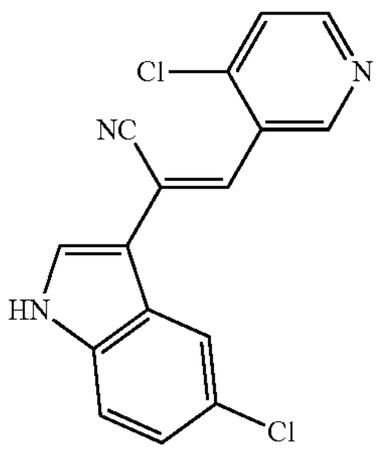
Method B: (Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile (50 mg), KOH (45 mg) and EtOH (1.5 mL). Trituration with AcOEt. Aspect of the pure product: yellow solid. (Yield: 67%).

ESI-MS: $(M+H)^+$=320

^{1}H NMR (Acetone-d_6, 300 MHz) δ ppm: 9.05 (s, 1H), 8.47 (d, J=5.8 Hz, 1H), 7.81 (s, 1H), 7.75 (s, 1H), 7.49 (d, J=2.3 Hz, 1H), 7.47 (d, J=9.0 Hz, 1H), 7.11 (d J=5.8 Hz, 1H), 6.93 (dd, J=9.0 Hz, J=2.3 Hz, 1H), 4.40 (q, J=7.0 Hz, 1H), 3.88 (s, 3H), 1.49 (t, J=7.0 Hz, 1H).

Example 3

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)acrylonitrile



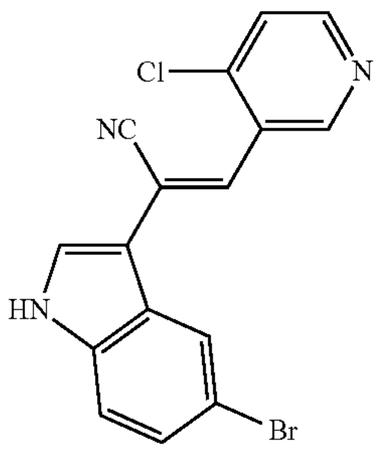
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (670 mg). Sodium hydride (138 mg). THF 17 mL. 4-chloronicotinaldehyde (457 mg). Trituration of the crude product with MeOH. Aspect of the pure product orange solid. (Yield: 38%)

ESI-MS: $(M+H)^+$=314

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 12.1 (s, 1H), 9.05 (s, 1H), 8. 6 (d, 1H), 8.06 (d, 1H), 8.03 (d, 1H), 7.8 (s, 1H), 7.75 (d, 1H), 7.57 (dd, 1H), 7.3 (dd, 1H).

Example 4

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-chloropyridin-3-yl)acrylonitrile



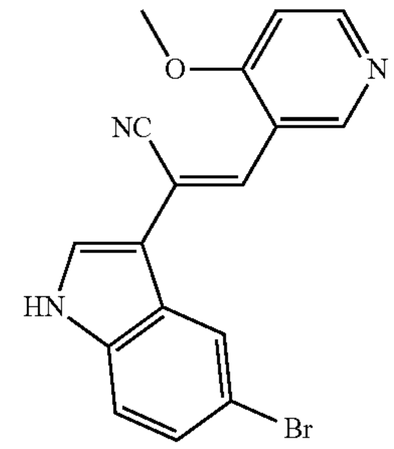
Method A: tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (600 mg). Sodium hydride (100 mg). THF 17 mL. 4-chloronicotinaldehyde (355 mg). Trituration of the crude product with dichloromethane and then washed with methanol and ether. Aspect of the pure product orange brown solid. (Yield: 50%)

ESI-MS: $(M+H)^+$=358

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 12.1 (s, 1H), 9.03 (s, 1H), 8. 62 (d, 1H), 8.2 (d, 1H), 8.0 (d, 1H), 7.8 (s, 1H), 7.76 (d, 1H), 7.55 (d, 1H), 7.4 (dd, 1H).

Example 5

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile



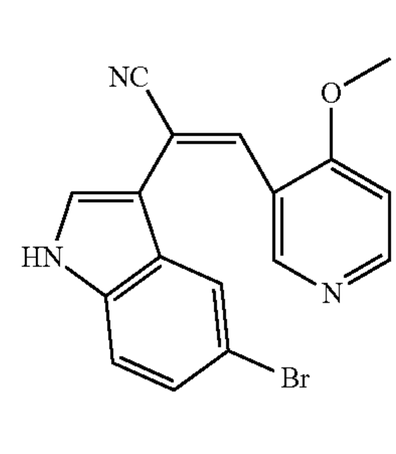
Method B: (Z)-2-(5-Bromo-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile (80 mg), 5 KOH (25 mg), MeOH (5 mL) and THF (2 mL). The mixture was refluxed for 24 hours. Purification by flash chromatography (CH_2Cl_2/MeOH 100/0 to 96/3). Aspect of the pure product: yellow solid. (Yield: 66%).

ESI-MS: $(M+H)^+$=354

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 11.96 (s, 1H), 8.83 (s, 1H), 8.52 (d, J=8.8 Hz, 1H), 8.09 (d, J=1.9 Hz, 1H), 7.90 (d, J=2.6 Hz, 1H), 7.68 (s, 1H), 7.48 (d, J=8.7 Hz, 1H), 7.36 (dd, J=8.7 Hz, J=1.9 Hz, 1H), 7.20 (d, J=5.8 Hz, 1H), 3.95 (s, 3H).

Example 5b

(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile



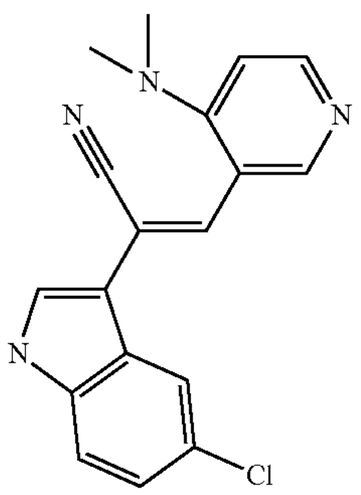
Method E: (Z)-2-(5-bromo-1H-indol-3-yl)-3-(2-methoxyphenyl)acrylonitrile (30 mg). EtOH (40 mL). Reaction time: 18 h. Aspect of the pure product: yellow solid. (Yield: 40%).

ESI-MS: $(M+H)^+$=354

^{1}H NMR (methanol-d4, 300 MHz) δ ppm: 8.31 (d, 1H), 8.00 (s, 1H), 7.55 (s, 1H), 7.42 (s, 1H), 7.35 (d, 1H), 7.26-7.14 (m, 2H), 6.96 (d, 1H), 4.00 (s, 3H).

Example 6

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(dimethylamino)pyridin-3-yl)acrylonitrile



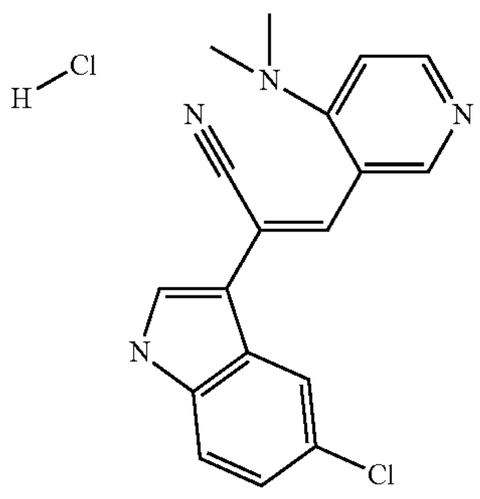
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (150 mg). Sodium hydride (28.9 mg). THF 2 mL. 4-dimethylaminonicotinaldehyde (93 mg). Trituration of the crude product with water and diisopropylether. Aspect of the product pale yellow solid (Yield: 82%)

APCI-MS: $(M+H)^+$=323

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 11.92 (s, 1H), 8.52 (s, 1H), 8.26 (d, J=5.8 Hz, 1H), 7.98 (d, J=1.9 Hz, 1H), 7.90 (s, 1H), 7.59 (s, 1H), 7.51 (d, J=8.7 Hz, 1H), 7.23 (dd, J=8.7, 1.9 Hz, 1H), 6.93 (d, J=5.9 Hz, 1H), 1.16-1.10 (m, 0.33H), 1.07 (t, J=7.0 Hz, 5.6H).

Example 7

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(dimethylamino)pyridin-3-yl)acrylonitrile, hydrochloride



In a 25 mL pear flask, (Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(dimethylamino)pyridin-3-yl)acrylonitrile (60 mg, 0.186 mmol) was dissolved in ethanol (1 mL) and dichloromethane (0.5 mL) to give a yellow solution followed by addition of HCl 37% in water (0.015 mL, 0.186 mmol).

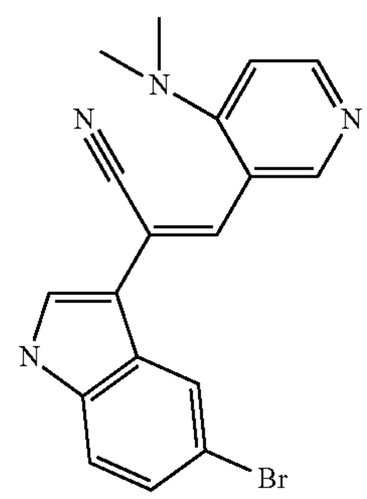
The reaction mixture was concentrated under reduce pressure to give 67 mg of a yellow solid (Yield: 100%)

APCI-MS: $(M+H)^+$=323

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 14.47-13.49 (m, 1H), 12.09 (s, 1H), 8.53 (s, 1H), 8.28 (d, J=7.3 Hz, 1H), 8.08 (s, 1H), 7.91 (s, 2H), 7.53 (d, J=8.7 Hz, 1H), 7.25 (d, J=10.6 Hz, 1H), 7.14 (d, J=7.3 Hz, 1H), 3.25 (s, 6H).

Example 8

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(dimethylamino)pyridin-3-yl)acrylonitrile



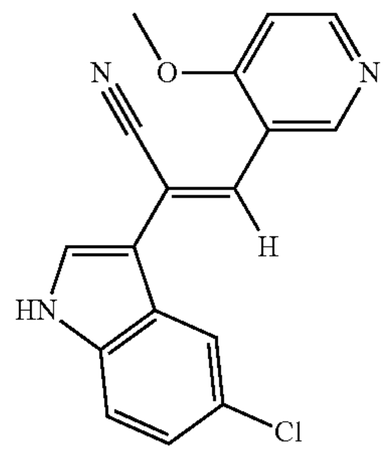
Method A: tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (150 mg). Sodium hydride (25 mg). THF 2 mL. 4-dimethylaminonicotinaldehyde (81 mg). Trituration of the crude product with water and ethanol. Aspect of the product pale yellow solid (Yield: 61%)

APCI-MS: $(M+H)^+$=367

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 11.92 (s, 0.9H), 11.85-11.77 (m, 0.1H), 8.51 (s, 1H), 8.26 (d, J=5.9 Hz, 1H), 8.10 (s, 1H), 7.88 (d, J=2.8 Hz, 1H), 7.62 (s, 1H), 7.46 (d, J=8.7 Hz, 1H), 7.39-7.28 (m, 1H), 6.89 (d, J=5.9 Hz, 1H), 2.92 (s, 5,6H), 2.85 (s, 0.4H).

Example 9

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile



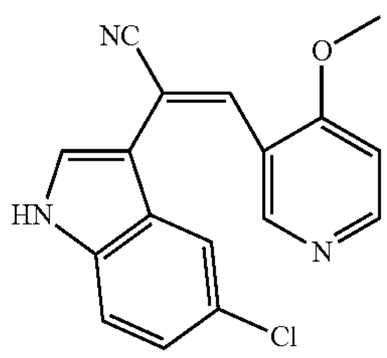
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (276 mg). THF 7 mL. Sodium hydride (57 mg), 4-methoxypyridine-3-carboxaldehyde (156 mg). Reaction time 24 hours. Trituration of the crude product with MeOH. Aspect of the pure product: orange solid. (Yield: 35%).

ESI-MS: $(M+H)^+$=310

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 11.97 (s, 1H), 8.82 (s, 1H), 8.51 (d, J=5.8 Hz, 1H), 7.94 (d, J=1.8 Hz, 1H), 7.91 (s, 1H), 7.68 (s, 1H), 7.52 (d, J=8.7 Hz, 1H), 7.24 (dd, J=8.7, 1.9 Hz, 1H), 7.19 (d, J=5.8 Hz, 1H), 3.94 (s, 3H).

Example 9b

(E)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile



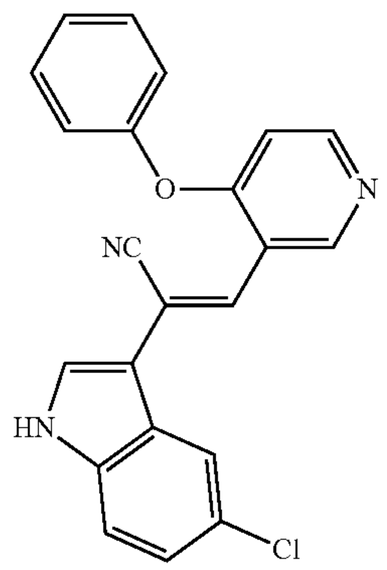
Method E: (Z)-2-(5-chloro-1H-indol-3-yl)-3-(2-methoxyphenyl)acrylonitrile (20 mg). EtOH (35 mL). Reaction time: 8 h. Aspect of the pure product: yellow solid. (Yield: 30%).

ESI-MS: $(M+H)^+$=310

^{1}H NMR (methanol-d4, 300 MHz) δ ppm: 8.31 (d, 1H), 8.01 (s, 1H), 7.56 (s, 1H), 7.42 (s, 1H), 7.38 (d, 1H), 7.16 (d, 1H), 7.10 (d, 1H), 6.83 (d, 1H), 4.00 (s, 3H).

Example 10

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-phenoxypyridin-3-yl)acrylonitrile



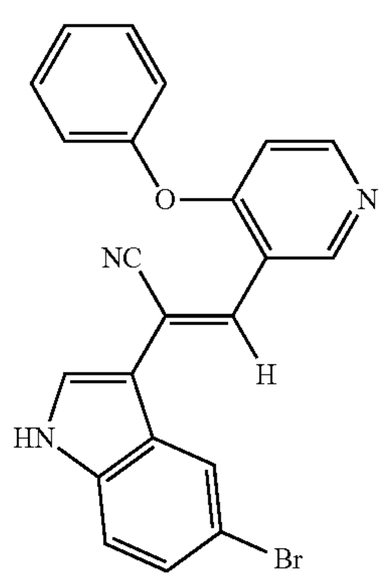
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (190 mg). THF 6 mL. Sodium hydride (40 mg), 4-phenoxypyridine-3-carboxaldehyde (160 mg). Reaction time 24 hours. The reaction mixture was not extracted. A precipitate was formed in the reaction mixture, filtered and washed with ether. Trituration of the precipitate with MeOH. Aspect of the pure product: yellow orange solid. (Yield: 73%).

ESI-MS: (M−H)=370

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 8.98 (s, 1H), 8.46 (d, J=5.7 Hz, 1H), 7.99 (s, 1H), 7.87 (s, 1H), 7.73 (s, 1H), 7.62 (d, 1H), 7.50 (m, 2H), 7.35-7.2 (m, 3H), 7.17 (dd, J=8.7, 1H), 6.75 (d, J=5.7 Hz, 1H).

Example 11

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-phenoxypyridin-3-yl)acrylonitrile



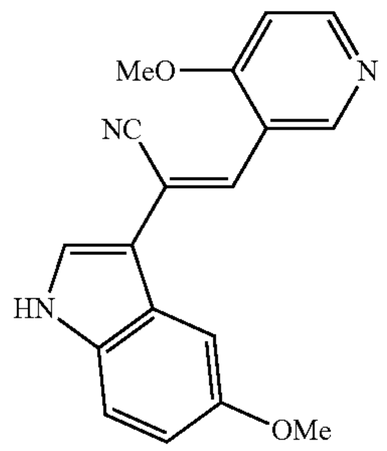
Method A: tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (224 mg). THF 4.9 mL. Sodium hydride (40 mg), 4-phenoxypyridine-3-carboxaldehyde (160 mg). Reaction time 24 hours. Trituration of the crude product with MeOH. Aspect of the pure product: yellow solid. (Yield: 18.7%).

ESI-MS: (M−H)=414

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 12.01 (s, 1H), 9.0 (s, 1H), 8.48 (d, J=5.7 Hz, 1H), 8.11 (d, J=1.7 Hz, 1H), 7.94 (s, 1H), 7.83 (s, 1H), 7.55-7.48 (m, 3H), 7.4-7.25 (m, 4H), 6.76 (d, J=5.7 Hz, 1H).

Example 12

(Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile



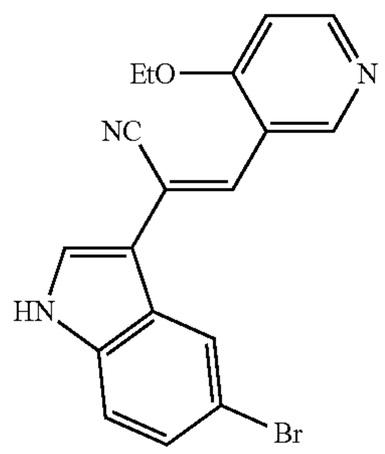
Method B: (Z)-2-(5-methoxy-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile (50 mg), KOH (45 mg) and MeOH (1.5 mL). Trituration with AcOEt. Aspect of the pure product: yellow solid. (Yield: 71%).

ESI-MS: $(M+H)^+$=306

^{1}H NMR (Acetone-d_6, 300 MHz) δ ppm: 9.02 (s, 1H), 8.50 (d, J=5.7 Hz, 1H), 7.77 (s, 1H), 7.75 (s, 1H), 7.50 (d, J=2.3 Hz, 1H), 7.46 (d, J=8.9 Hz, 1H), 7.14 (d, J=5.7 Hz, 1H), 6.93 (dd, J=8.9 Hz, J=2.3 Hz, 1H), 4.03 (s, 3H), 3.87 (s, 3H).

Example 13

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-ethoxypyridin-3-yl)acrylonitrile



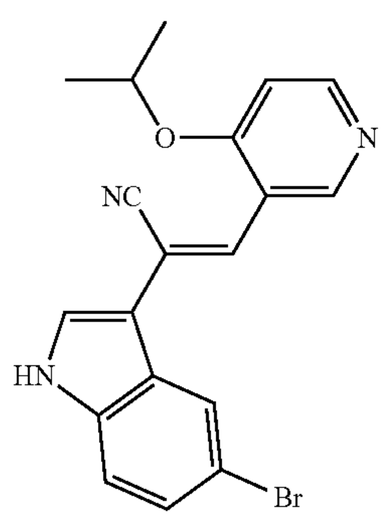
Method B: (Z)-2-(5-Bromo-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile (40 mg), KOH (31 mg), EtOH (5 mL). Trituration with AcOEt. Aspect of the pure product: yellow solid. (Yield: 76%).

ESI-MS: $(M+H)^+$=368

^{1}H NMR (acetone-d_6, 300 MHz) δ ppm: 9.06 (s, 1H), 8.49 (d, J=5.5 Hz, 1H), 8.20 (s, 1H), 7.85 (s, 1H), 7.55 (d, J=8.5 Hz, 1H), 7.40 (d, J=8.2 Hz, 1H), 7.12 (d, J=5.8 Hz, 1H), 4.31 (q, J=7.0 Hz, 2H), 1.54 (t, J=7.0 Hz, 3H).

Example 14

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-isopropoxypyridin-3-yl)acrylonitrile



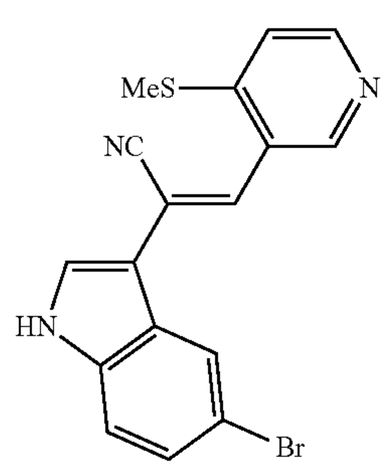
Method B: (Z)-2-(5-Bromo-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile (70 mg), KOH (55 mg), isopropanol (2 mL). Purification by flash chromatography (CH_2Cl_2/MeOH 100/0 to 95/5). Aspect of the pure product: yellow solid. (Yield: 20%).

ESI-MS: $(M+H)^+$=382

^{1}H NMR (MeOD, 300 MHz) δ ppm: 9.02 (s, 1H), 8.42 (d, J=5.8 Hz, 1H), 8.09 (d, J=1.5 Hz, 1H), 7.75 (s, 1H), 7.69 (s, 1H), 7.42 (d, J=8.7 Hz, 1H), 7.36 (dd, J=8.7 Hz, J=1.5 Hz, 1H), 7.19 (d, J=5.8 Hz, 1H), 4.93 (sept, J=6.0 Hz, 1H), 1.50 (d, J=6.0 Hz, 6H).

Example 15

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(methylthio)pyridin-3-yl)acrylonitrile



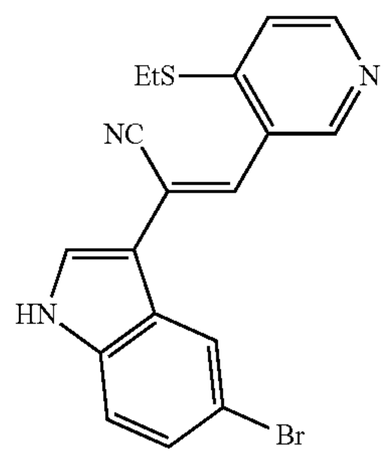
Method C: (Z)-2-(5-Bromo-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile (80 mg), NaSMe (31 mg), DMF (1 mL). Aspect of the pure product: yellow solid. (Yield: 61%).

ESI-MS: $(M+H)^+$=370

^{1}H NMR (acetone-d_6, 300 MHz) δ ppm: 11.12 (s, 1H), 8.83 (s, 1H), 8.48 (d, J=5.3 Hz, 1H), 8.24 (d, J=1.9 Hz, 1H), 7.91 (s, 1H), 7.67 (s, 1H), 7.57 (d, J=8.7 Hz, 1H), 7.41 (dd, J=8.7 Hz, J=1.9 Hz, 1H), 7.39 (d, J=5.3 Hz, 1H), 2.66 (s, 3H).

Example 16

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(ethylthio)pyridin-3-yl)acrylonitrile



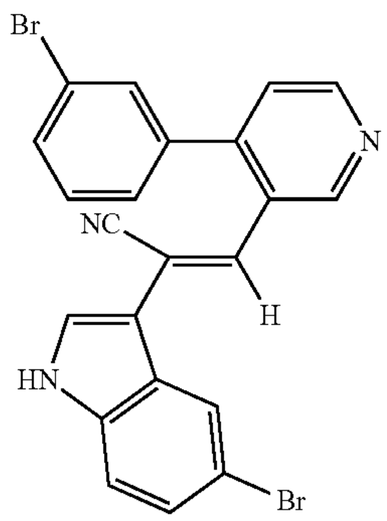
Method C: (Z)-2-(5-Bromo-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile (80 mg), NaSEt (37 mg), DMF (1 mL). Aspect of the pure product: yellow solid. (Yield: 70%).

ESI-MS: $(M+H)^+$=384

^{1}H NMR (acetone-d_6, 300 MHz) δ ppm: 11.13 (s, 1H), 8.86 (s, 1H), 8.47 (d, J=5.5 Hz, 1H), 8.26 (d, J=1.7 Hz, 1H), 7.91 (s, 1H), 7.68 (s, 1H), 7.56 (d, J=8.7 Hz, 1H), 7.45-7.39 (m, 2H), 3.21 (q, J=7.5 Hz, 2H), 1.42 (t, J=7.5 Hz, 3H).

Example 17

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(3-bromophenyl)pyridin-3-yl)acrylonitrile



Method A: tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (300 mg). THF 6.6 mL. Sodium hydride (54 mg), 4-(3-bromophenyl)-3-pyridinecarboxaldehyde (328 mg). Reaction time 24 hours. Trituration of the crude product with MeOH. Aspect of the pure product: yellow solid. (Yield: 65%).

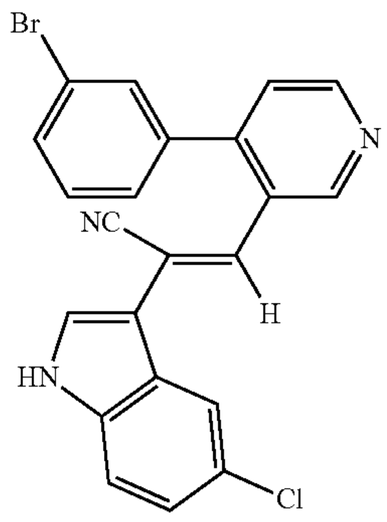
ESI-MS: $(M+H)^+$=478

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 11.96 (s, 1H), 9.04 (s, 1H), 8.72 (d, 1H), 7.84 (s, 1H), 7.79-7.68 (m, 3H), 7.65-7.43 (m, 5H), 7.32 (dd, 1H).

Example 18

(Z)-3-(4-(3-bromophenyl)pyridin-3-yl)-2-(5-chloro-1H-indol-3-yl)acrylonitrile

Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (266 mg). THF 6.8 mL. Sodium hydride (55 mg), 4-(3-bromophenyl)-3-pyridinecarboxaldehyde (336 mg). Reaction time 24 hours. Trituration of the crude product with MeOH. Aspect of the pure product: yellow solid. (Yield: 52%).

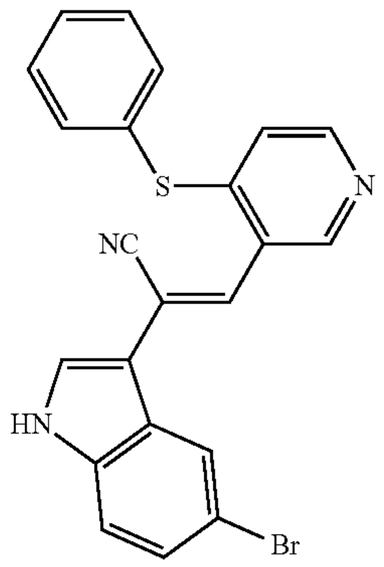


ESI-MS: $(M+H)^+$=434

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 11.96 (s, 1H), 9.04 (s, 1H), 8.72 (d, 1H), 7.86 (s, 1H), 7.81-7.68 (m, 3H), 7.66-7.46 (m, 5H), 7.22 (dd, 1H).

Example 19

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(phenylthio)pyridin-3-yl)acrylonitrile



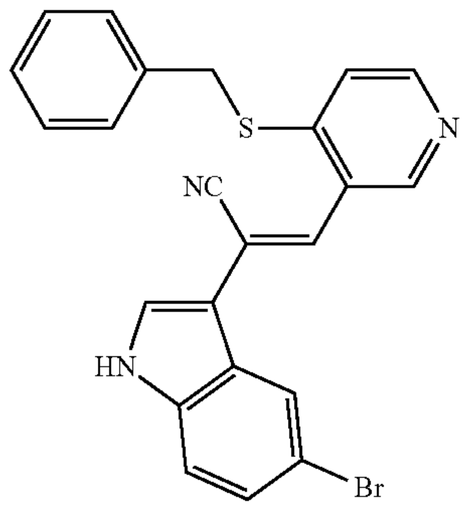
Method D: (Z)-2-(5-Bromo-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile (80 mg), thiophenol (25 μl), sodium carbonate (47 mg), DMF (1 mL). Aspect of the pure product: yellow solid. (Yield: 53%).

ESI-MS: $(M+H)^+$=432

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 12.05 (s, 1H), 8.81 (s, 1H), 8.40 (d, J=5.3 Hz, 1H), 8.15 (d, J=1.7 Hz, 1H), 7.96 (s, 1H), 7.73 (s, 1H), 7.62 (m, 2H), 7.55 (m, 3H), 7.50 (d, J=8.7 Hz, 1H), 7.38 (dd, J=8.7 Hz, J=1.7 Hz, 1H), 6.81 (d, J=5.3 Hz, 1H).

Example 20

(Z)-3-(4-(benzylthio)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)acrylonitrile



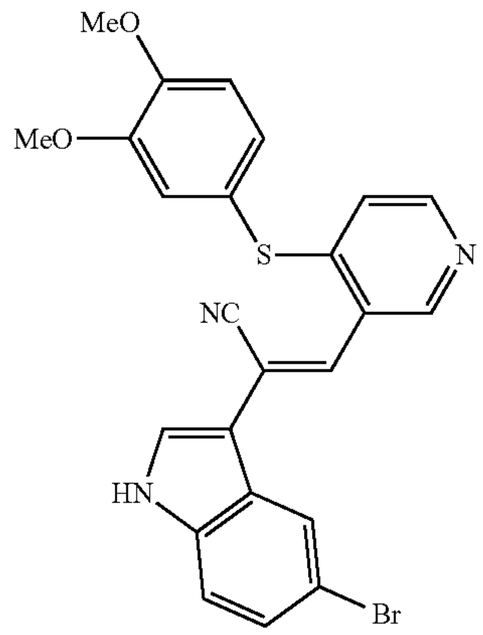
Method D: (Z)-2-(5-Bromo-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile (50 mg), benzyl mercaptan (18 μL), sodium carbonate (30 mg), DMF (1 mL). Aspect of the pure product: yellow solid. (Yield: 47%).

ESI-MS: $(M+H)^+$=446

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 12.01 (s, 1H), 8.73 (s, 1H), 8.58 (d, J=5.2 Hz, 1H), 8.12 (d, J=1.2 Hz, 1H), 7.92 (s, 1H), 7.60 (s, 1H), 7.56 (d, J=5.2 Hz, 1H), 7.49-7.47 (m, 3H), 7.37-7.33 (m, 3H), 7.28 (m, 1H), 4.47 (s, 2H).

Example 21

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-((3,4-dimethoxyphenyl)thio)pyridin-3-yl)acrylonitrile



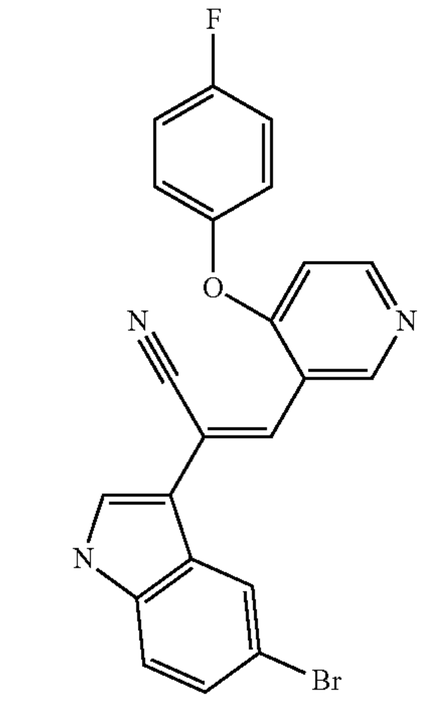
Method D: (Z)-2-(5-Bromo-1H-indol-3-yl)-3-(4-chloro-3-yl)acrylonitrile (61 mg), 3,4-dimethoxythiophenol (37 μL), sodium carbonate (36 mg), DMF (1 mL). Aspect of the pure product: yellow solid. (Yield: 50%).

ESI-MS: $(M+H)^+$=492

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 12.05 (s, 1H), 8.76 (s, 1H), 8.36 (d, J=5.2 Hz, 1H), 8.17 (s, 1H), 7.96 (s, 1H), 7.70 (s, 1H), 7.51 (d, J=8.5 Hz, 1H), 7.39 (d, J=8.5 Hz, 1H), 7.22 (d, J=8.2 Hz, 1H), 7.19 (s, 1H), 7.13 (d, J=8.5 Hz, 1H), 6.74 (d, J=5.2 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H).

Example 22

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-fluorophenoxy)pyridin-3-yl)acrylonitrile



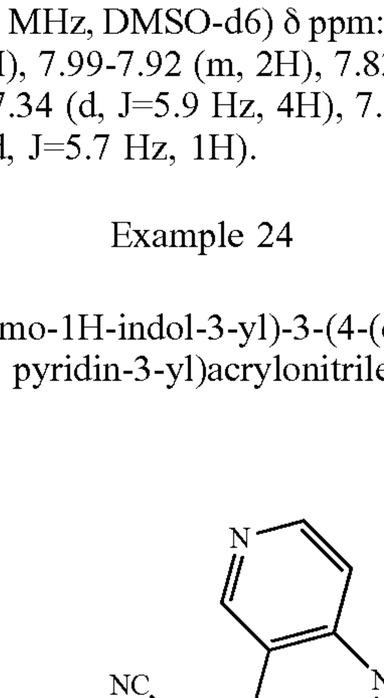
Method A: tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (200 mg). THF 2 mL. Sodium hydride (31.7 mg), 4-(4-fluorophenyl)-3-pyridinecarboxaldehyde (148 mg). Reaction time 1 h 30. Trituration of the crude product with DCM. Aspect of the product: yellow solid. (Yield: 10%).

LC-MS: (M+H)+=434

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 12.01 (s, 1H), 8.98 (s, 1H), 8.46 (d, J=5.7 Hz, 1H), 8.11 (d, J=1.7 Hz, 1H), 7.94 (s, 1H), 7.83 (s, 1H), 7.48 (d, J=8.7 Hz, 1H), 7.38-7.31 (m, 5H), 6.73 (d, J=5.7 Hz, 1H).

Example 23

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(4-fluorophenoxy)pyridin-3-yl)acrylonitrile



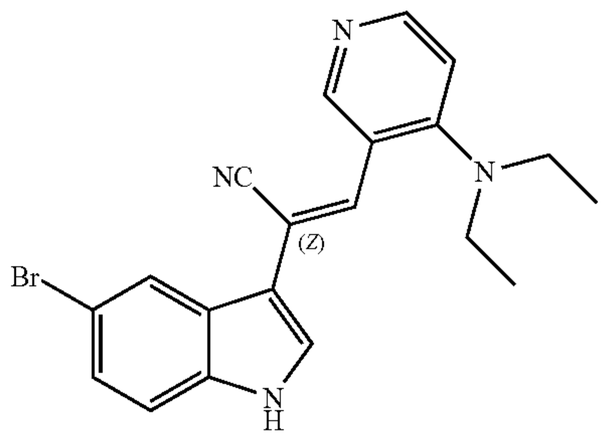
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (200 mg). THF 2 mL. Sodium hydride (35.1 mg), 4-(4-fluorophenyl)-3-pyridinecarboxaldehyde (163 mg). Reaction time 1 hour 30 minutes. Trituration of the crude product with DCM. Aspect of the product: yellow solid. (Yield: 82%).

APCI-MS: $(M+H)^+$=390

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 8.98 (s, 1H), 8.46 (d, J=5.7 Hz, 1H), 7.99-7.92 (m, 2H), 7.83 (s, 1H), 7.52 (d, J=8.7 Hz, 1H), 7.34 (d, J=5.9 Hz, 4H), 7.24 (dd, J=8.7, 1.8 Hz, 1H), 6.73 (d, J=5.7 Hz, 1H).

Example 24

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(diethylamino)pyridin-3-yl)acrylonitrile



Method A: Aspect of the product: yellow solid (Yield: 60%)

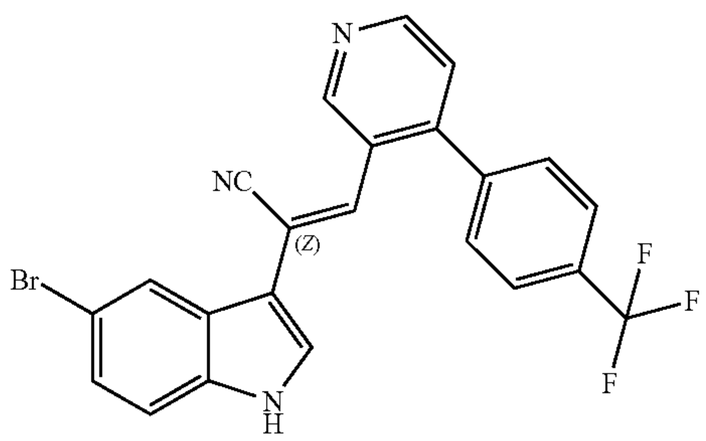
APCI-MS: $(M+H)^+$=395

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 11.93 (s, 0.83H), 11.88-11.76 (m, 0.12H), 8.52 (s, 1H), 8.27 (d, J=5.8 Hz, 1H),

8.12 (d, J=1.7 Hz, 1H), 7.88 (s, 1H), 7.59 (s, 1H), 7.51-7.21 (m, 2H), 6.93 (d, J=5.9 Hz, 1H), 3.32-3.24 (m, 4H), 1.07 (t, J=7.0 Hz, 6H).

Example 25

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(4-(trifluoromethyl)phenyl)pyridin-3-yl)acrylonitrile



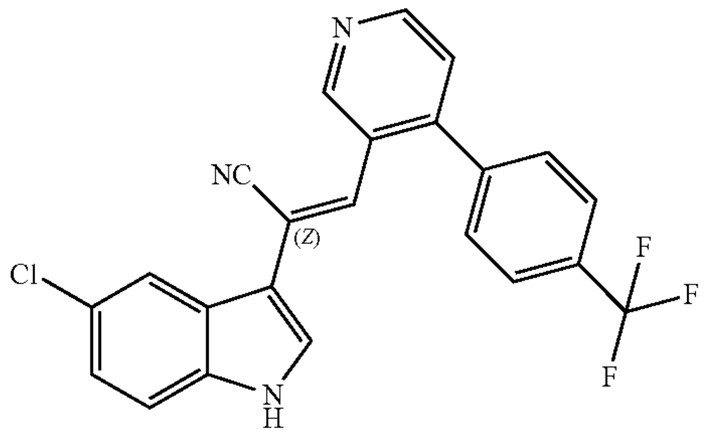
Method A: tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (120 mg). THF 3 mL. Sodium hydride (20.05 mg), 4-(4-trifluoromethylphenyl)-3-pyridinecarboxaldehyde (108 mg). Reaction time 16 hours. Purification by chromatography on 24 g Redisep column 20-40 μm, eluted with a gradient of CH_2Cl_2/MeOH from 100/00 to 95/05. Dissolution of the solid in EtOH (3 mL) and water (0.3 mL) and concentration in a Genevac evaporator to remove the traces of solvent. Aspect of the product: yellow solid. (Yield: 57%).

APCI-MS: $(M+H)^+$=468

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 12.19-11.57 (s, 1H), 9.11 (s, 1H), 8.80-8.61 (d, 1H), 7.66 (, m, 11H).

Example 26

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(4-(trifluoromethyl)phenyl)pyridin-3-yl)acrylonitrile



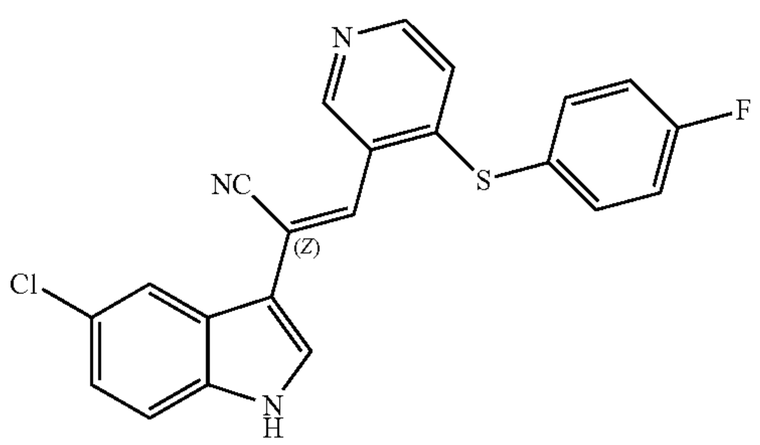
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (120 mg). THF 3 mL. Sodium hydride (23.11 mg), 4-(4-trifluoromethylphenyl)-3-pyridinecarboxaldehyde (124 mg). Reaction time 16 hours. Purification by chromatography on 24 g Redisep column 20-40 μm, eluted with a gradient of CH_2Cl_2/MeOH from 100/00 to 95/05. Dissolution of the solid in EtOH (3 mL) and water (0.3 mL) and concentration in a Genevac evaporator to remove the traces of solvent. Aspect of the product: yellow solid. (Yield: 68%).

APCI-MS: $(M+H)^+$=424

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 12.40-11.44 (m, 1H), 9.10 (s, 1H), 8.73 (d, J=5.1 Hz, 1H), 7.91-7.16 (m, 11H).

Example 27

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-((4-fluorophenyl)thio)pyridin-3-yl)acrylonitrile



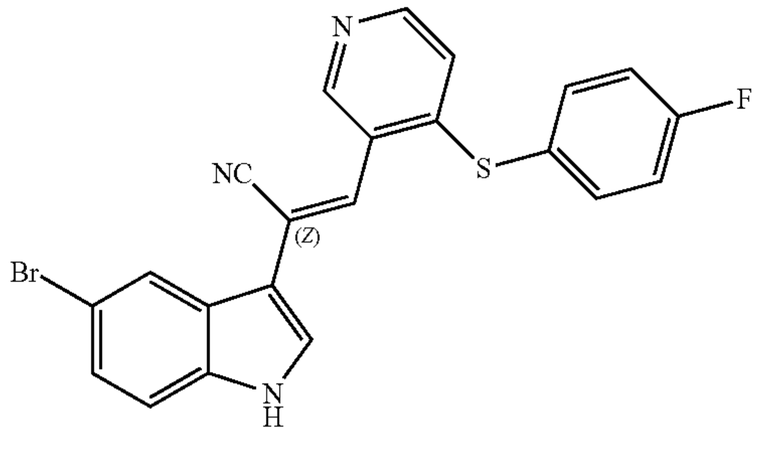
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (150 mg). THF 2 mL. Sodium hydride (28.9 mg), 4-(4-fluorophenylthio)-3-pyridinecarboxaldehyde (144 mg). Reaction time 16 hours. Trituration of the crude product with heptane and diisopropylether. Aspect of the product: yellow solid. (Yield: 42%).

APCI-MS: $(M+H)^+$=406

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 8.79 (s, 1H), 8.38 (d, J=5.4 Hz, 1H), 7.97 (s, 2H), 7.68 (s, 4H), 7.56 (d, J=8.6 Hz, 1H), 7.42 (d, J=8.6 Hz, 3H), 7.26 (s, 1H), 6.76 (d, J=5.4 Hz, 1H).

Example 28

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(44(4-fluorophenyl)thio)pyridin-3-yl)acrylonitrile



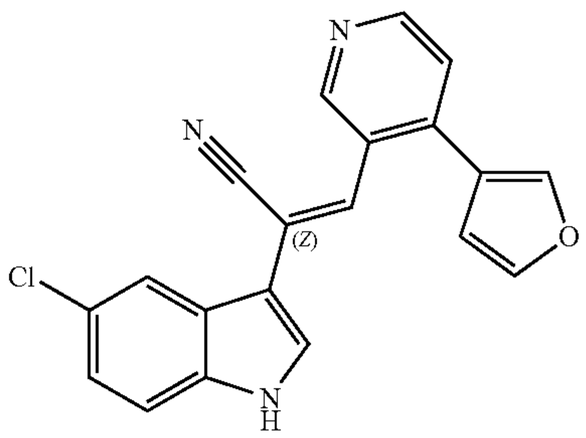
Method A: tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (150 mg). THF 2 mL. Sodium hydride (25.06 mg), 4-(4-fluorophenylthio)-3-pyridinecarboxaldehyde (125 mg). Reaction time 16 hours. Trituration of the crude product with heptane and ether. Aspect of the product: yellow solid. (Yield: 32%).

APCI-MS: $(M+H)^+$=450

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 11.98(s1, 1H), 8.82-8.74 (m, 1H), 8.43-8.35 (m, 1H), 8.18-8.13 (m, 1H), 7.99-7.93 (m, 1H), 7.70 (dd, J=8.6, 2.7 Hz, 3H), 7.44 (qd, J=8.6, 7.1 Hz, 4H), 6.80-6.73 (m, 1H).

Example 29

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(furan-3-yl) pyridin-3-yl)acrylonitrile



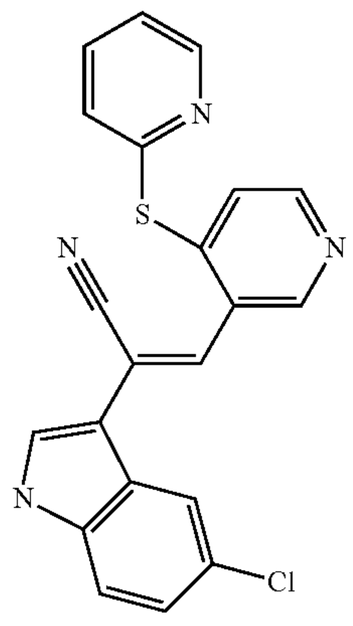
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (150 mg). THF 3 mL. Sodium hydride (17.33 mg), 4-(furan-3-yl)nicotinaldehyde 107 mg). Reaction time 16 hours. Trituration of the crude product with heptane and diisopropylether. Aspect of the product: yellow solid. (Yield: 21%).

APCI-MS: $(M+H)^+$=346

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 11.99 (s, 1H), 8.93 (s, 1H), 8.64 (d, J=5.2 Hz, 1H), 8.10 (s, 1H), 8.01-7.92 (m, 2H), 7.87 (s, 1H), 7.77 (s, 1H), 7.64 (d, J=5.1 Hz, 1H), 7.53 (d, J=8.7 Hz, 1H), 7.25 (dd, J=8.7, 1.9 Hz, 1H), 6.97 (s, 1H).

Example 30

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-(pyridin-2-yl-thio)pyridin-3-yl)acrylonitrile



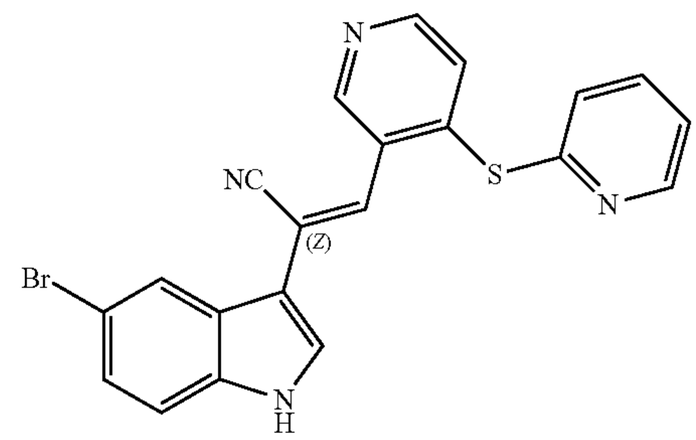
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (150 mg). THF 2 mL. Sodium hydride (28.9 mg), 4-(piridin-2-yl)thio-nicotinaldehyde (134 mg). Reaction time 16 hours. Trituration of the crude product with heptane and diisopropylether. Aspect of the product: yellow solid. (Yield: 55%).

APCI-MS: $(M+H)^+$=389

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 9.00 (s, 1H), 8.60-8.52 (m, 1H), 8.48 (d, J=3.8 Hz, 1H), 7.86 (s, 1H), 7.81-7.73 (m, 1H), 7.68 (s, 1H), 7.59 (s, 1H), 7.52 (d, J=5.3 Hz, 2H), 7.43 (d, J=7.9 Hz, 1H), 7.28 (dd, J=7.0, 5.2 Hz, 1H), 7.20-7.12 (m, 1H).

Example 31

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(pyridin-2-yl-thio)pyridin-3-yl)acrylonitrile

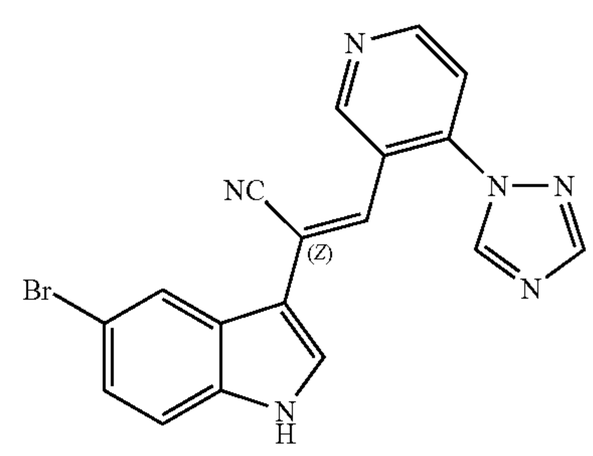


Method A: tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (150 mg). THF 2 mL. Sodium hydride (25.06 mg), 4-(piridin-2-yl)thio-nicotinaldehyde (116 mg). Reaction time 16 hours. Trituration of the crude product with heptane and ether. Aspect of the product: yellow solid. (Yield: 65%).

APCI-MS: $(M+H)^+$=433 ^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 9.00 (s, 1H), 8.62-8.57 (m, 1H), 8.52-8.46 (m, 1H), 7.91-7.86 (m, 2H), 7.78 (ddd, J=9.5, 7.7, 1.8 Hz, 1H), 7.68 (s, 1H), 7.56-7.52 (m, 1H), 7.49-7.42 (m, 2H), 7.37-7.26 (m, 2H).

Example 32

(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-bromo-1H-indol-3-yl)acrylonitrile



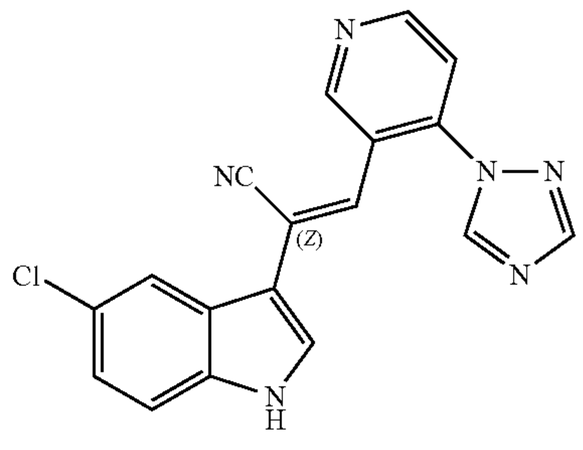
Method A: tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (150 mg). THF 2 mL. Sodium hydride (25.06 mg), 4-(1H-1,2,4-triazol-1-yl)nicotinaldehyde (118 mg). Reaction time 16 hours. Trituration of the crude product with ethanol. Aspect of the product: yellow solid. (Yield: 32%).

APCI-MS: $(M+H)^+$=391

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 12.00 (s, 1H), 9.28 (s, 1H), 9.14 (s, 1H), 8.81 (d, 1H), 8.37 (s, 1H), 8.10 (s, 1H), 7.87 (s, 3H), 7.52-7.29 (m, 2H).

Example 33

(Z)-3-(4-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-chloro-1H-indol-3-yl)acrylonitrile



Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (150 mg). THF 5 mL. Sodium hydride (28.9 mg), 4-(1H-1,2,4-triazol-1-yl)nicotinaldehyde (136 mg). Reaction time 16 hours. Purification by flash chromatography on 24 g Redisep column 20-40 μm, gradient 100% CH_2Cl_2 to CH_2Cl_2/MeOH (90/10). Aspect of the product: yellow solid. (Yield: 33%).

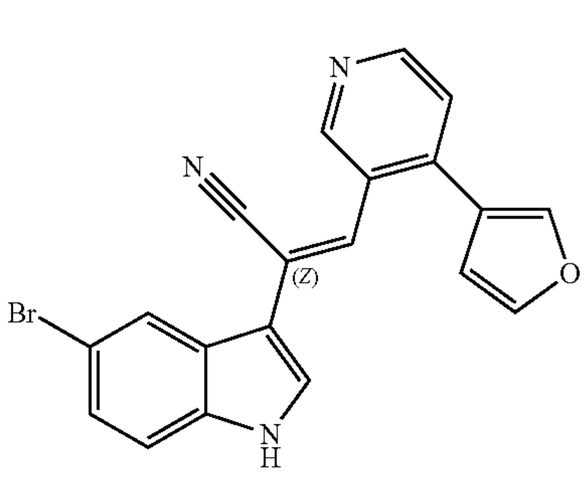
Aspect of the product: yellow solid (Yield: 33%)

APCI-MS: $(M+H)^+$=347

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 12.32-11.49 (m, 1H), 9.27 (s, 1H), 9.15 (d, J=4.0 Hz, 1H), 8.82 (d, J=5.4 Hz, 1H), 8.66-8.57 (m, 0.1H), 8.46-8.25 (m, 1H), 8.03-7.71 (m, 4H), 7.59-7.35 (m, 1H), 7.25 (dd, J=8.7, 2.0 Hz, 1H).

Example 34

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)acrylonitrile



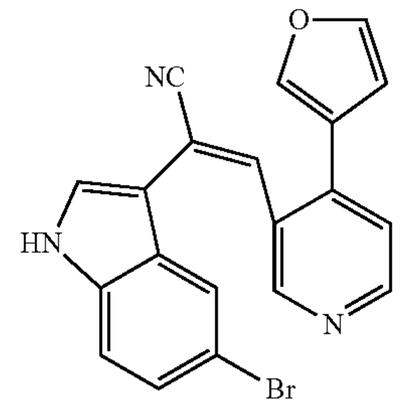
Method A: tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (150 mg). THF 3 mL. Sodium hydride (15.03 mg), 4-(furan-3-yl)nicotinaldehyde (93 mg). Reaction time 16 hours. Trituration of the crude product with water and NaOH. Aspect of the product: yellow solid. (Yield: 27%).

APCI-MS: $(M+H)^+$=390

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 11.98 (s, 1H), 8.92 (s, 1H), 8.64 (d, J=5.2 Hz, 1H), 8.13-8.06 (m, 2H), 7.92 (d, J=2.7 Hz, 1H), 7.87 (t, J=1.7 Hz, 1H), 7.76 (s, 1H), 7.63 (d, J=5.1 Hz, 1H), 7.48 (d, J=8.7 Hz, 1H), 7.35 (dd, J=8.7, 1.8 Hz, 1H), 6.96 (d, J=1.0 Hz, 1H).

Example 34b

(E)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)acrylonitrile



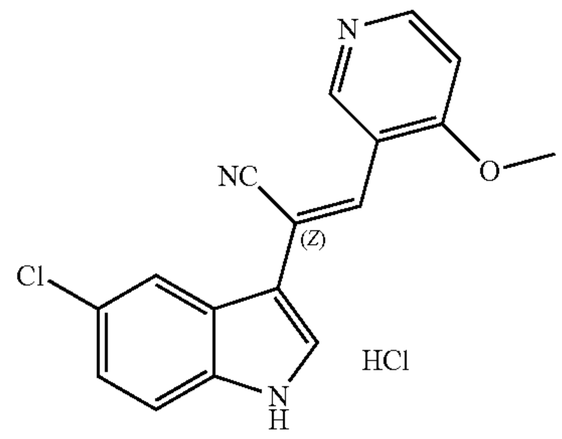
Method E: (Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)acrylonitrile (20 mg). EtOH (40 mL). Reaction time: 8 h. Aspect of the pure product: yellow solid. (Yield: 60%).

ESI-MS: $(M+H)^+$=390

^{1}H NMR (methanol-d4, 300 MHz) δ ppm: 8.37 (d, 1H), 8.19 (s, 1H), 8.0 (s, 1H), 7.72 (s, 1H), 7.60 (d, 1H), 7.45 (s, 1H), 7.38 (s, 1H), 7.30 (d, 1H), 7.19 (d, 1H), 6.98 (s, 1H), 6.89 (s, 1H).

Example 35

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile, hydrochloride



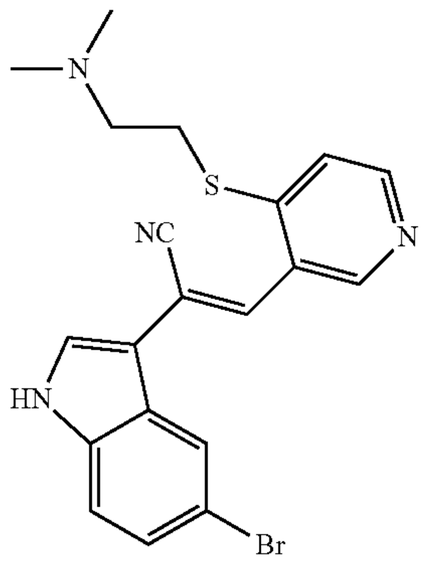
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (300 mg). THF 5 mL. Sodium hydride (57.8 mg), 4-methoxynicotinaldehyde (170 mg). Reaction time 16 hours. Trituration of the crude product with DCM and 4N HCl in dioxane. Aspect of the product: yellow solid. (Yield: 81%).

APCI-MS: $(M+H)^+$=310

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 12.18 (s, 1H), 9.12 (s, 1H), 8.86 (d, J=6.8 Hz, 1H), 7.99 (d, J=3.1 Hz, 2H), 7.71 (d, J=6.8 Hz, 1H), 7.64 (s, 1H), 7.55 (d, J=8.7 Hz, 1H), 7.27 (dd, J=8.7, 1.9 Hz, 1H), 4.16 (s, 3H).

Example 36

(Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-42-dimethyl-amino)ethypthio)pyridin-3-yl)acrylonitrile



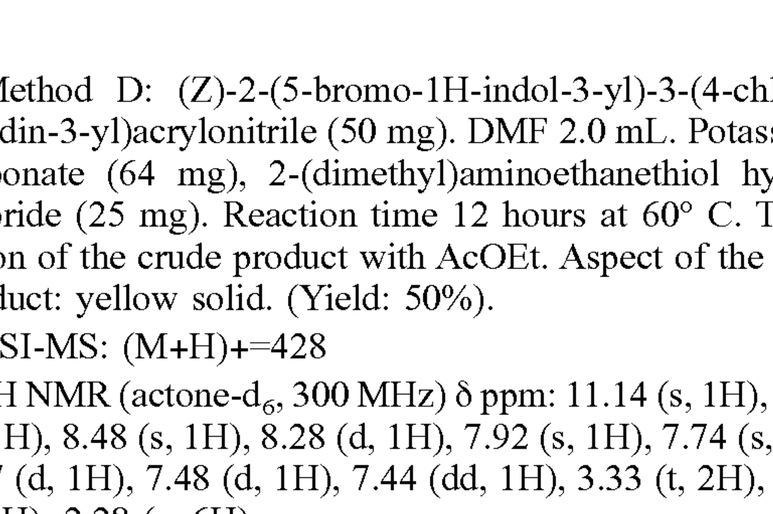
Method D: (Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-chloro-pyridin-3-yl)acrylonitrile (50 mg). DMF 2.0 mL. Potassium carbonate (64 mg), 2-(dimethyl)aminoethanethiol hydrochloride (25 mg). Reaction time 12 hours at 60° C. Trituration of the crude product with AcOEt. Aspect of the pure product: yellow solid. (Yield: 50%).

ESI-MS: (M+H)+=428

^{1}H NMR (actone-d_6, 300 MHz) δ ppm: 11.14 (s, 1H), 8.86 (s, 1H), 8.48 (s, 1H), 8.28 (d, 1H), 7.92 (s, 1H), 7.74 (s, 1H) 7.57 (d, 1H), 7.48 (d, 1H), 7.44 (dd, 1H), 3.33 (t, 2H), 2.70 (t, 2H), 2.28 (s, 6H).

Example 37

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(4-fluorophenoxy)benzonitrile



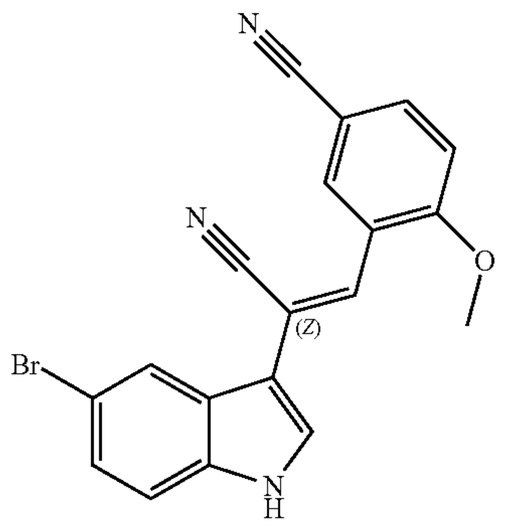
Method A: tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (100 mg). THF 2.0 mL. Sodium hydride (16.71 mg), 3-cyano-4-fluorophenoxy-benzaldehyde (102 mg). Reaction time 1 hour 30 minutes. Purification by flash chromatography, eluent petroleum ether/MTBE. Aspect of the pure product: yellow solid. (Yield: 48%).

APCI-MS: (M−H)=456

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 12.02 (s, 1H), 8.39 (s, 1H), 8.05 (s, 1H), 7.93 (s, 1H), 7.86 (d, J=6.6 Hz, 1H), 7.81 (s, 1H), 7.47 (d, J=8.7 Hz, 1H), 7.32 (dd, J=15.3, 7.0 Hz, 5H), 6.95 (d, J=8.7 Hz, 1H).

Example 38

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile



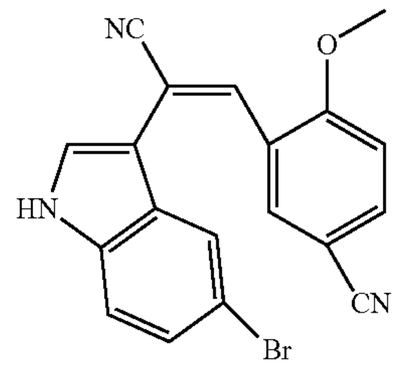
Method A: Tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (150 mg, 0.447 mmol) THF 2 mL, NaH (25.06 mg, 0.626 mmol), 3-formyl-4-methoxybenzonitrile (88 mg, 0.537 mmol). Reaction time 1 hour 30 minutes. The reaction mixture diluted with water (20 mL). The resulting solid was filtered, washed successively with water, CH_2Cl_2, DIPE and acetonitrile and dried in vacuo to give 55 mg of a yellow solid (Yield: 30%)

APCI-MS: (M−H)=376

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.99 (s, 1H), 8.22 (s, 1H), 8.08 (s, 1H), 7.91 (s, 2H), 7.70 (s, 1H), 7.60-7.15 (m, 3H), 3.97 (s, 3H).

Example 38b

(E)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile



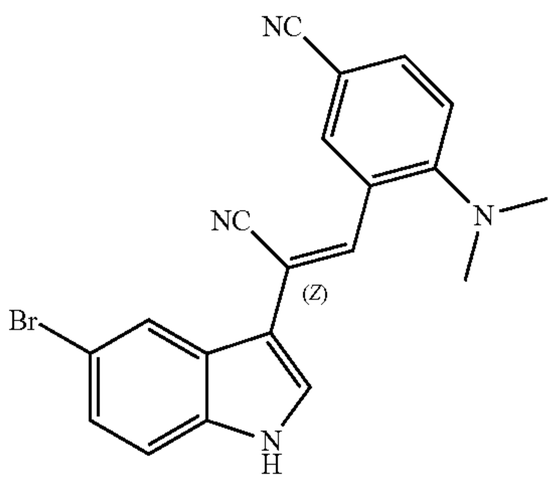
Method E: (Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (20 mg). EtOH (40 mL). Reaction time: 8 h. Aspect of the pure product: yellow solid. (Yield: 60%).

ESI-MS: $(M+H)^+$=379

^{1}H NMR (methanol-d4, 300 MHz) δ ppm: 7.61 (d, 1H), 7.49 (s, 1H), 7.36 (s, 1H), 7.32 (d, 1H), 7.26-7.13 (m, 3H), 6.85 (d, 1H), 3.91 (s, 3H).

Example 39

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile



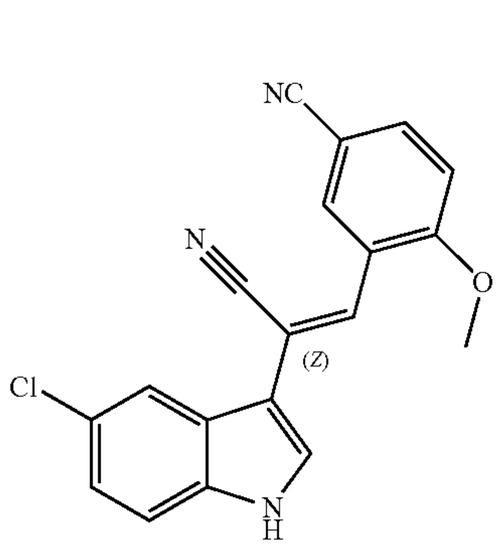
Method A: tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (120 mg). THF 2.5 mL. Sodium hydride (11.55 mg), 3-cyano-4-dimethylamino-benzaldehyde (73.3 mg). Reaction time 16 hours. Silical gel flash-column chromatography (eluent heptane/ethyl acetate. Aspect of the purified product: yellow solid. (Yield: 33%).

APCI-MS: $(M+H)^+$=391

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.98 (s, 1H), 8.10 (d, J=1.6 Hz, 1H), 8.05 (d, J=1.7 Hz, 1H), 7.91 (s, 1H), 7.75 (dd, J=8.6, 2.1 Hz, 1H), 7.56 (s, 1H), 7.48 (d, J=8.7 Hz, 1H), 7.35 (dd, J=8.7, 1.8 Hz, 1H), 7.16 (d, J=8.7 Hz, 1H), 2.89 (s, 6H).

Example 40

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile



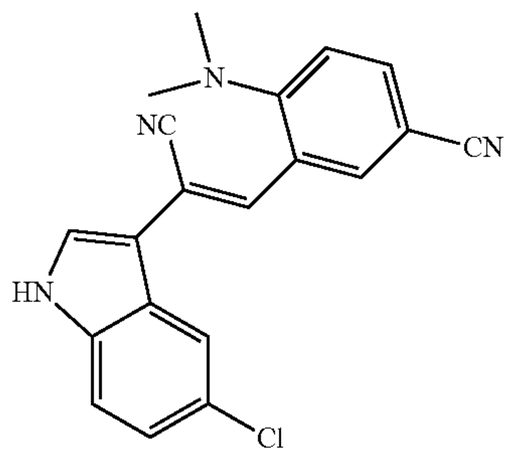
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (200 mg). THF 2.0 mL. Sodium hydride (35.1 mg), 3-cyano-4-methoxybenzaldehyde (124 mg). Reaction time 1 hour 30 minutes. Silical gel flash-column chromatography (petroleum ether/DIPE) and trituration of the purified product with acetonitrile. Aspect of the pure product: yellow solid. (Yield: 40%).

APCI-MS: (M−H)=332

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 8.21 (s, 1H), 7.93 (d, J=6.5 Hz, 3H), 7.70 (s, 1H), 7.52 (d, J=8.7 Hz, 1H), 7.29 (dd, J=22.2, 9.6 Hz, 2H), 3.96 (s, 3H).

Example 41

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile



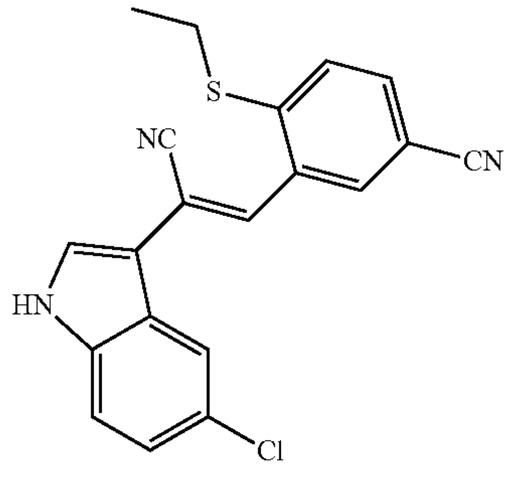
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (200 mg). THF 2.0 mL. Sodium hydride (35.1 mg), 3-cyano-4-dimethylaminobenzaldehyde (134 mg). Reaction time 1 hour 30 minutes. Silical gel flash-column chromatography (petroleum ether/DIPE) and trituration of the purified product with acetonitrile. Aspect of the pure product: yellow solid. (Yield: 33%).

APCI-MS: (M+H)+=347

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.95 (s, 1H), 8.04 (d, J=1.7 Hz, 1H), 8.00-7.89 (m, 2H), 7.75 (dd, J=8.6, 2.0 Hz, 1H), 7.62-7.45 (m, 2H), 7.30-7.09 (m, 2H), 2.89 (s, 6H).

Example 42

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(ethylthio)benzonitrile



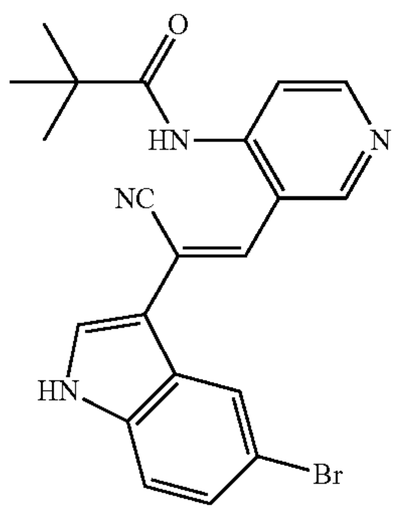
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (200 mg). THF 2.0 mL. Sodium hydride (35.1 mg), 3-cyano-4-ethylthiobenzaldehyde (145 mg). Reaction time 1 hour 30 minutes. Silical gel flash-column chromatography (petroleum ether/DIPE) and trituration of the purified product with acetonitrile. Aspect of the pure product: yellow solid. (Yield: 36%).

APCI-MS: (M−H)=362

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 12.04 (s, 1H), 8.12 (s, 1H), 8.04-7.92 (m, 2H), 7.87 (dd, J=8.3, 1.7 Hz, 1H), 7.72-7.58 (m, 2H), 7.54 (d, J=8.7 Hz, 1H), 7.27 (dd, J=8.7, 1.9 Hz, 1H), 3.18 (q, J=7.3 Hz, 2H), 1.31 (t, J=7.3 Hz, 3H).

Example 43

(Z)—N-(3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)pyridin-4-yl)pivalamide



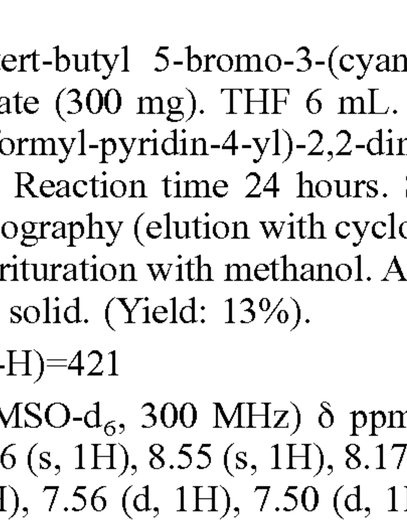
Method A: tert-butyl 5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (300 mg). THF 6 mL. Sodium hydride (54 mg), N-(formyl-pyridin-4-yl)-2,2-dimethyl-propionamide (258 mg). Reaction time 24 hours. Silical gel flash-column chromatography (elution with cycloheptane/AcOEt: 1/1 to 1/9) and trituration with methanol. Aspect of the pure product: yellow solid. (Yield: 13%).

ESI-MS: (M−H)=421

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 11.98 (s, 1H), 9.49 (s, 1H), 8.96 (s, 1H), 8.55 (s, 1H), 8.17 (d, 1H), 7.88 (d, 1H), 7.68 (s, 1H), 7.56 (d, 1H), 7.50 (d, 1H), 1.25 (s, 9H).

Example 44

(Z)—N-(3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)pyridin-4-yl)pivalamide



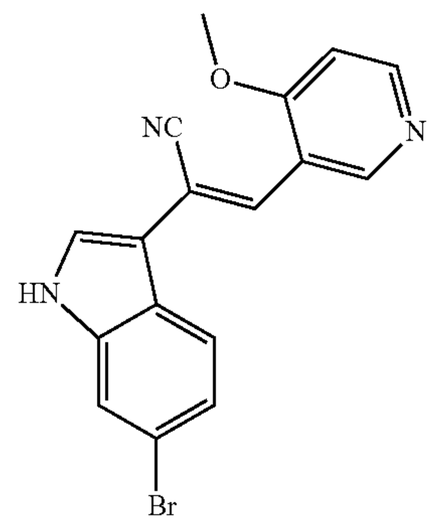
Method A: tert-butyl 5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (300 mg). THF 6 mL. Sodium hydride (62 mg), N-(formyl-pyridin-4-yl)-2,2-dimethyl-propionamide (298 mg). Reaction time 24 hours. Silical gel flash-column chromatography (elution with cycloheptane/AcOEt: 1/1 to 1/9) of the residue afforded the corresponding acrylonitrile as a yellow solid (Yield: 18%).

ESI-MS: (M+H)$^+$=379

^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm: 11.98 (s, 1H), 9.49 (s1, 1H), 8.96 (s, 1H), 8.55 (s, 1H), 8.17 (s, 1H), 7.85 (s, 1H), 7.68 (s, 1H), 7.56 (m, 1H), 7.25 (d, 1H), 1.22 (s, 9H).

Example 45

(Z)-2-(6-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile



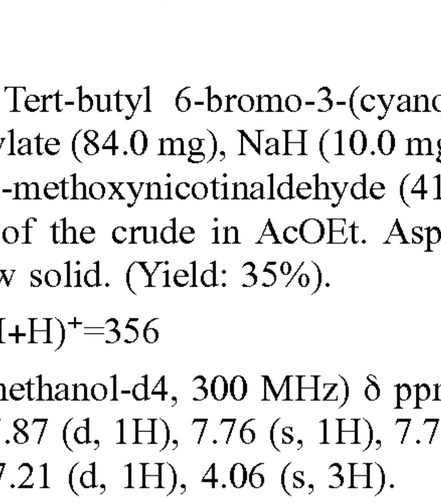
Method F: Tert-butyl 6-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (84.0 mg), NaH (10.0 mg). THF (2 mL). 10 min at rt. 4-methoxynicotinaldehyde (41.0 mg). 12 h at rt. Trituration of the crude in AcOEt. Aspect of the pure product: yellow solid. (Yield: 35%).

ESI-MS: (M+H)$^+$=356

^{1}H NMR (methanol-d4, 300 MHz) δ ppm: 8.95 (s, 1H), 8.47 (d, 1H), 7.87 (d, 1H), 7.76 (s, 1H), 7.70-7.65 (m, 2H), 7.33 (d, 1H), 7.21 (d, 1H), 4.06 (s, 3H).

Example 46

(Z)-2-(6-fluoro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile



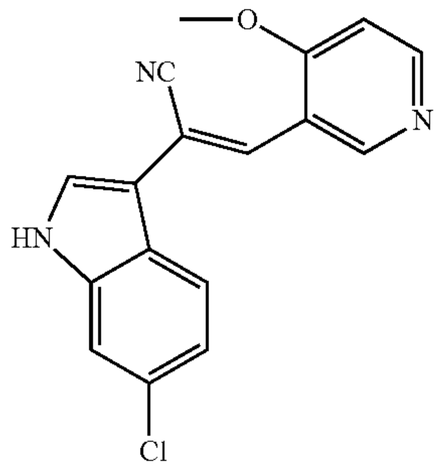
Method F: Tert-butyl 6-fluoro-3-(cyanomethyl)-1H-indole-1-carboxylate (98.0 mg), NaH (18.0 mg). THF (3 mL). 10 min at rt. 4-methoxynicotinaldehyde (58.0 mg). 12 h at rt. Trituration of the crude in AcOEt. Aspect of the pure product: yellow solid. (Yield: 43%).

ESI-MS: (M+H)$^+$=294

^{1}H NMR (methanol-d4, 300 MHz) δ ppm: 8.30 (d, 1H), 8.00 (s, 1H), 7.55 (s, 1H), 7.41 (s, 1H), 7.38 (d, 1H), 7.16 (d, 1H), 7.10 (dd, 1H), 6.82 (d, 1H), 4.00 (s, 3H).

Example 47

(Z)-2-(6-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile



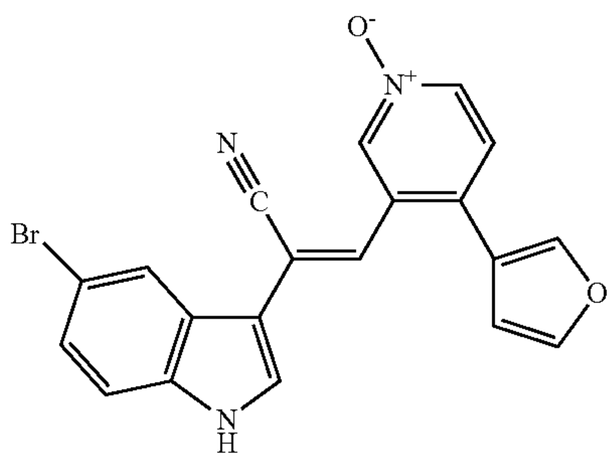
Method F: Tert-butyl 6-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (100.0 mg), NaH (18.0 mg). THF (3 mL). 10 min at rt. 4-methoxynicotinaldehyde (56.0 mg). 12 h at rt. NaOH 2.5 M (1.5 mL). 12 h at rt. Trituration of the crude in AcOEt. Aspect of the pure product: yellow solid. (Yield: 42%).

ESI-MS: $(M+H)^+$=310

^{1}H NMR (methanol-d4, 300 MHz) δ ppm: 8.95 (s, 1H), 8.48 (d, 1H), 7.92 (d, 1H), 7.76 (s, 1H), 7.71 (s, 1H), 7.50 (d, 1H), 7.24-7.18 (m, 2H), 4.06 (s, 3H).

Example 48

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(furan-3-yl)pyridine-1-oxide



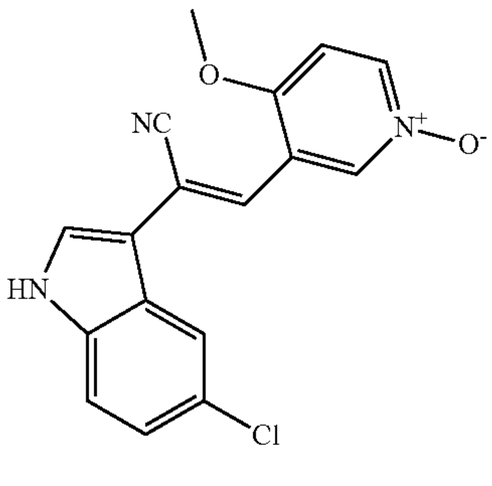
Method G: (Z)-2-(5-bromo-1H-indol-3-yl)-3-(4-(furan-3-yl)pyridin-3-yl)acrylonitrile (30.0 mg), m-CPBA (28.0+15.0 mg). THF (1.0 mL). 16 h at room temperature. Trituration of the crude in AcOEt. Aspect of the pure product: yellow solid. (Yield: 72%).

ESI-MS: $(M+H)^+$=408

^{1}H NMR (methanol-d4, 300 MHz) δ ppm: 8.83 (s, 1H), 8.37 (d, 1H), 8.03 (s, 1H), 8.01-7.92 (m, 2H), 7.82 (s, 1H), 7.79-7.72 (m, 1H), 7.66-7.56 (m, 2H), 7.54-7.33 (m, 1H), 6.86 (s, 1H).

Example 49

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxypyridine 1-oxide



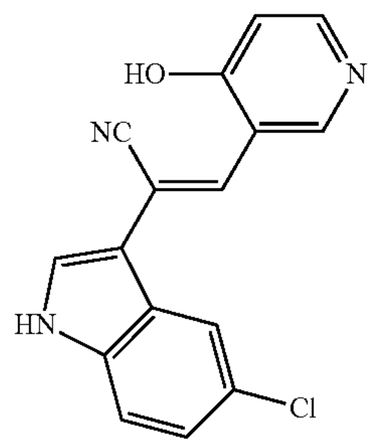
Method G: (Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile (30.0 mg), m-CPBA (33.0+16.0 mg). THF (1.5 mL). 16 h at room temperature. Trituration of the crude in AcOEt. Aspect of the pure product: yellow solid. (Yield: 80%).

ESI-MS: $(M+H)^+$=326

^{1}H NMR (methanol-d4, 300 MHz) δ ppm: 8.84 (s, 1H), 8.33 (d, 1H), 7.94 (s, 1H), 7.81 (s, 1H), 7.59 (s, 1H), 7.50 (d, 1H), 7.35 (d, 1H), 7.26 (d, 1H), 4.11 (s, 3H).

Example 50

(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-hydroxypyridin-3-yl)acrylonitrile



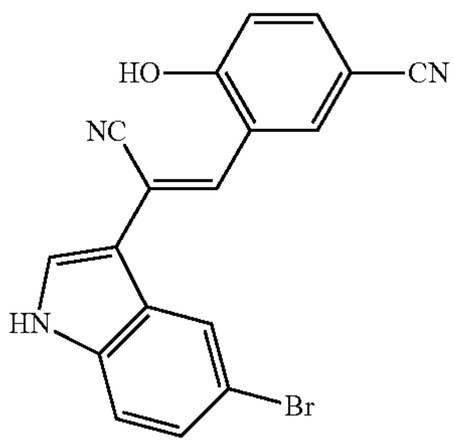
To a solution of (Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile (30.0 mg, 1 eq) in NMP (0.2 mL) were added LiCl (41.0 mg, 10 eq) and p-Toluenesulfonic acid (166.0 mg, 10 eq). The resulting mixture was stirred 1 h 30 at 180° C. then cooled to room temperature and extracted with AcOEt. The combined organic layers were washed with water and dried over Na_2SO_4, filtrated and concentrated. The residue was taken off with a minimal amount of AcOEt and filtrated to give 18.0 mg of the title compound (Yield: 95%).

ESI-MS: $(M+H)^+$=297

^{1}H NMR (methanol-d4, 300 MHz) δ ppm: 9.02 (s, 1H), 8.58 (d, 1H), 8.35 (s, 1H), 8.19 (s, 1H), 8.08 (d, 1H), 7.50-7.38 (m, 2H), 7.23 (d, 1H).

Example 51

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-hydroxybenzonitrile



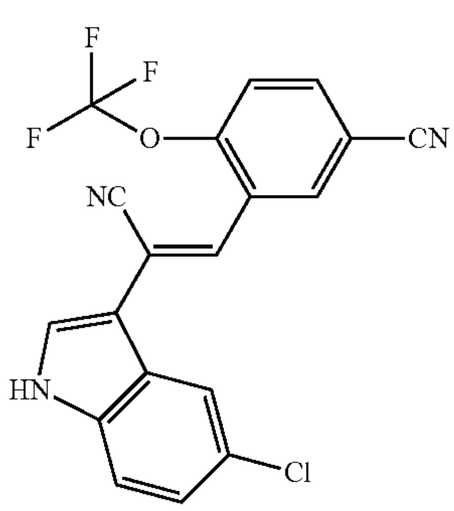
To a solution of (Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (30.0 mg, 1 eq) in NMP (0.2 mL) were added LiCl (33.0 mg, 10 eq) and p-Toluenesulfonic acid (136.0 mg, 10 eq). The resulting mixture was stirred 1 h 30 at 180 ° C. then cooled to room temperature and extracted with AcOEt. The combined organic layers were washed with water and dried over Na_2SO_4, filtrated and concentrated. The residue was purified by silicagel chromatography (CH_2Cl_2/MeOH, 100:0 to 90:10) to give 15.0 mg of the title compound (Yield: 52%).

ESI-MS: $(M+H)^+$=366

^{1}H NMR (methanol-d4, 300 MHz) δ ppm: 8.27 (s, 1H), 8.18 (s, 1H), 7.90-7.53 (m, 2H), 7.53 (d, 1H), 7.45-7.13 (m, 3H).

Example 52

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile



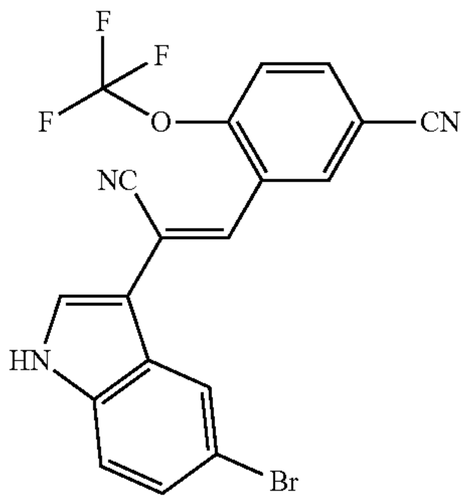
Method H: tert-butyl-5-chloro-3-(cyanomethyl)-1H-indole-1-carboxylate (1 eq), NaH (3 eq), 3-formyl-4-(trifluoromethoxy)benzonitrile (1 eq). Room temperature hidden from light. Aspect of the pure product: yellow solid. (Yield: 20%).

ESI-MS: $(M+H)^+$=387

^{1}H NMR (methanol-d4, 300 MHz) δ ppm: 8.49 (d, 1H), 7.92 (d, 1H), 7.83 (s, 1H), 7.68 (s, 1H), 7.82 (s, 1H), 7.58-7.42 (m, 2H), 7.28 (d, 1H).

Example 53

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile



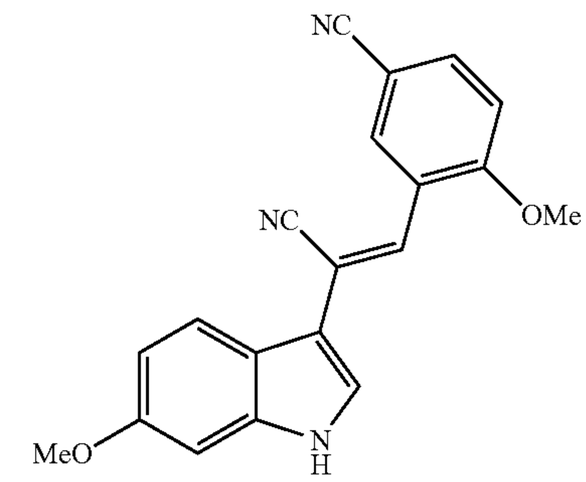
Method H: tert-butyl-5-bromo-3-(cyanomethyl)-1H-indole-1-carboxylate (1 eq), NaH (3 eq), 3-formyl-4-(trifluoromethoxy)benzonitrile (1 eq). Room temperature hidden from light. Aspect of the pure product: yellow solid. (Yield: 39%).

ESI-MS: $(M+H)^+$=433

^{1}H NMR (methanol-d4, 300 MHz) δ ppm: 8.48 (s, 1H), 8.07 (s, 1H), 7.91 (d, 1H), 7.80 (s, 1H), 7.66 (s, 1H), 7.49-7.35 (m, 3H).

Example 54

(Z)-3-(2-cyano-2-(6-methoxy-1H-indol-3-yl)vinyl)-4-methoxybenzonitrile



Method A: tert-butyl 3-(cyanomethyl)-6-methoxy-1H-indole-1-carboxylate (175 mg), 3-formyl-4-methoxybenzonitrile (103 mg), NaH (34 mg), THF (2 ml). Reaction time 2 hours at RT. Poured in water, extracted with Ethyl acetate and trituration with diethyl ether. Aspect of the pure product: yellow solid. (Yield: 18%)

APCI-MS: $(M+H)^+$=330

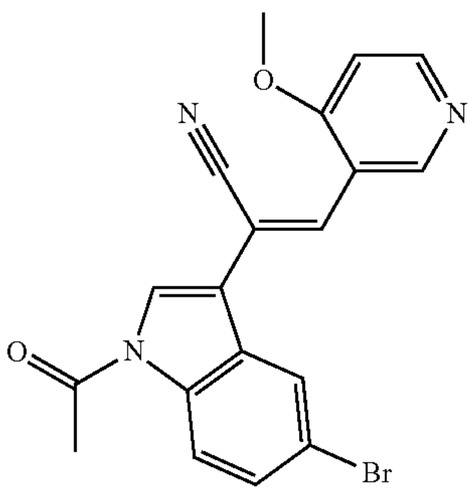
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 11.61 (s, 1H), 8.23 (d, J=1.7 Hz, 1H), 7.93 (dd, J=8.7, 2.0 Hz, 1H), 7.79 (d, J=8.8 Hz, 1H), 7.69 (s, 2H), 7.32 (d, J=8.7 Hz, 1H), 6.98 (d, J=2.2 Hz, 1H), 6.84 (dd, J=8.8, 2.2 Hz, 1H), 3.97 (s, 3H), 3.80 (s, 3H).

Some compounds of the previous examples have been the subject of tests which have demonstrated their specific relevance as inhibitors of MKlp2, and their cytotoxic effects on human cancer cells.

Preparation of Examples 55 to 79

Example 55

(Z)-2-(1-acetyl-5-bromo-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile



To a solution of (Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile (50.0 mg, 1 eq) in THF (4 mL) were added pyridine (1 mL), NEt_3 (0.085 mL, 4.5 eq), DMAP (8.8 mg, 0.5 eq) and acetyl chloride (0.044 mL, 3.6 eq). The resulting mixture was stirred 48 h at RT, then neutralized with saturated NH_4Cl and extracted with AcOEt. The combined organic layers were washed with water and dried over Na_2SO_4, filtrated and concentrated. The residue was taken off with a minimal amount of MeOH and filtrated to give the title compound as an orange solid (36.0 mg, 65%).

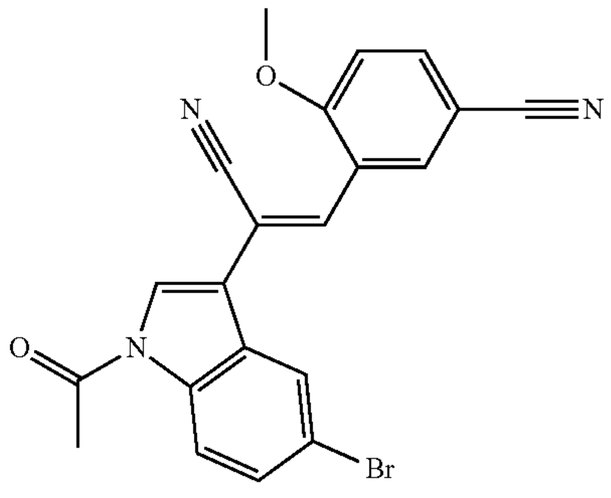
ESI-MS: $(M+H)^+$=396

^1H NMR (300 MHz, $CDCl_3$) δ ppm 9.12 (s, 1H), 8.62 (d, J=5.3 Hz, 1H), 8.47 (d, J=8.9 Hz, 1H), 8.05 (d, J=1.9 Hz, 1H), 7.84 (s, 1H), 7.81 (s, 1H), 7.58 (dd, J=8.9 Hz, 1.9 Hz, 1H), 6.98 (s, 1H), 4.04 (s, 3H), 2.73 (s, 3H).

The following example was prepared as the previous method.

Example 56

(Z)-3-(2-(1-acetyl-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile



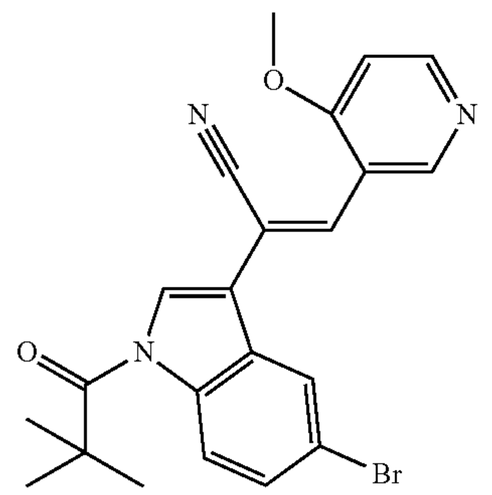
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (30 mg), THF (2.4 ml), pyridine (0.6 mL), NEt_3 (0.051 mL, 4.5 eq), DMAP (5.3 mg, 0.5 eq) and acetyl chloride (0.027 mL, 3.6 eq). Reaction time 48 hours. Extracted with AcOEt, precipitated with MeOH. Aspect of the pure product: yellow solid. (Yield: 40%).

ESI-MS: $(2M)^+$=839

^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.30 (d, J=1.7 Hz, 1H), 8.08 (d, J=1.7 Hz, 1H), 7.83-7.79 (m, 1H), 7.78 (s, 1H), 7.73 (s, 1H), 7.45-7.35 (m, 2H), 7.30 (s, 1H), 7.27 (s, 1H), 4.06 (s, 3H), 2.76 (s, 3H).

Example 57

(Z)-2-(5-bromo-1-pivaloyl-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile



To a solution of (Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile (30.0 mg, 1 eq) in THF (1 mL) was added NaH (6.7 mg, 2 eq). The mixture was stirred 10 min at room temperature and pivaloyl chloride (0.011 mL, 1.1 eq) was added. The resulting solution was stirred 3 h at room temperature, poured in saturated NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtrated and concentrated to give the title compound as a white solid (37.0 mg, 100%).

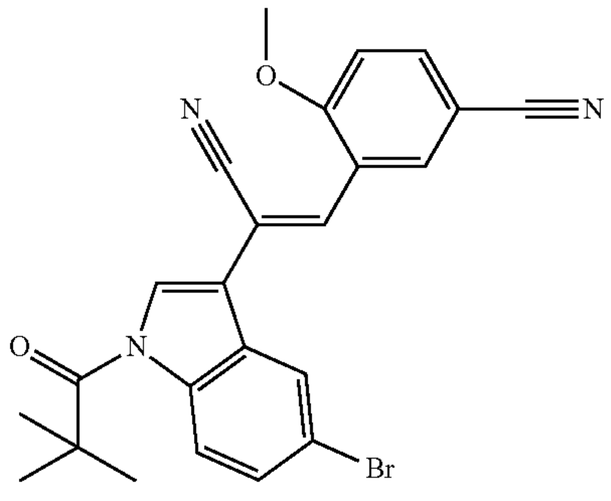
ESI-MS: $(M+H)^+$=438

^1H NMR (300 MHz, CD_3OD) δ ppm 9.20 (s, 1H), 8.82 (d, J=6.8 Hz, 1H), 8.45 (d, J=9.0 Hz, 1H), 8.35 (s, 1H), 8.13 (d, J=1.9 Hz, 1H), 7.88 (s, 1H), 7.68 (d, J=6.8 Hz, 1H), 7.60 (dd, J=9.0 Hz, 1.9 Hz, 1H), 4.30 (s, 3H), 1.57 (s, 9H).

The following examples were prepared as the previous method.

Example 58

(Z)-3-(2-(5-bromo-1-pivaloyl-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile



(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (500 mg), THF (16 ml), NaH 60% in oil (0.105 g, 2 eq), pivaloyl chloride (0.216 mg, 1.35 eq).

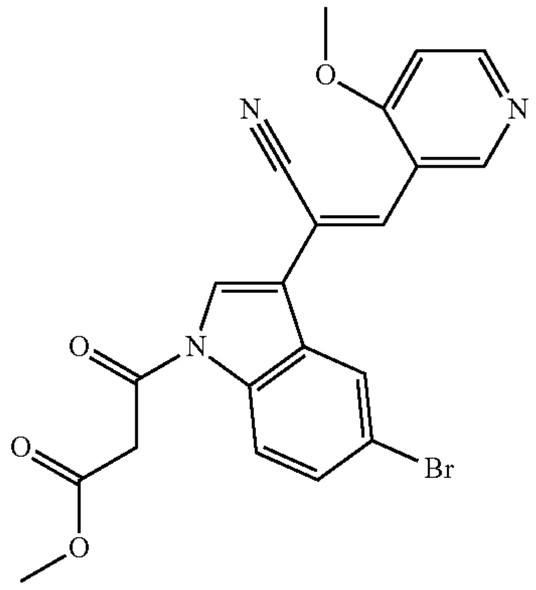
Reaction time 12 hours. Poured into AcOEt. Aspect of the pure product: white solid. (Yield: 100%).

ESI-MS: $(M+H)^+$=462

^{1}H NMR (300 MHz, DMSO-D6) δ ppm 8.39 (s, 1H), 8.36 (s, 1H), 8.27 (s, 1H), 8.12 (s, 1H), 8.01 (dd, J=8.9 Hz, 1.5 Hz, 1H), 7.97 (s, 1H), 7.61 (dd, J=8.9 Hz, 1.5 Hz, 1H), 7.38 (d, J=8.9 Hz, 1H), 3.98 (s, 3H), 1.50 (s, 9H).

Example 59

(Z)-methyl-3-(5-bromo-3-(1-cyano-2-(4-methoxypyridin-3-ypvinyl)-1H-indol-1-yl)-3-oxopropanoate



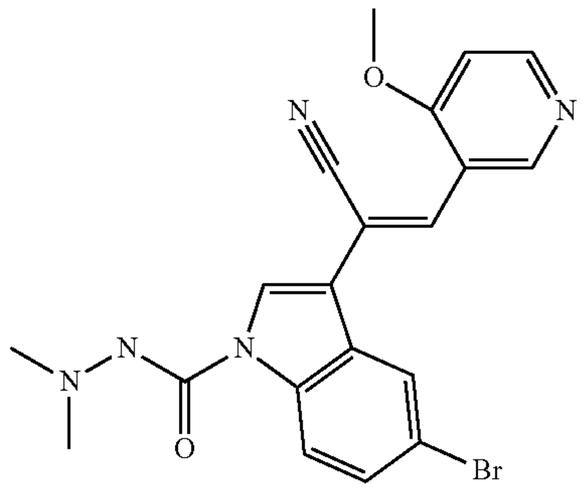
(Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile (100.0 mg), THF (4 mL), NaH 60% in oil (0.01 g, 1 eq), methylmalonyl chloride (0.042 g, 1.1 eq). Reaction time: 12 hours. Purification by silicagel chromatography CH_2Cl_2/MeOH (100:0 to 90:10). Aspect of the pure product: yellow solid. (Yield: 72%).

ESI-MS: $(M+H)^+$=454

^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.95 (s, 1H), 8.49 (s, 1H), 8.07 (s, 1H), 7.76-7.60 (m, 2H), 7.48-7.29 (m, 2H), 7.22 (s, 1H), 4.07 (s, 3H), 3.96 (s, 3H), 3.85 (s, 2H).

Example 60

(Z)-5-bromo-3-(1-cyano-2-(4-methoxypyridin-3-yl) vinyl)-N',N'-dimethyl-1H-indole-1-carbohydrazide



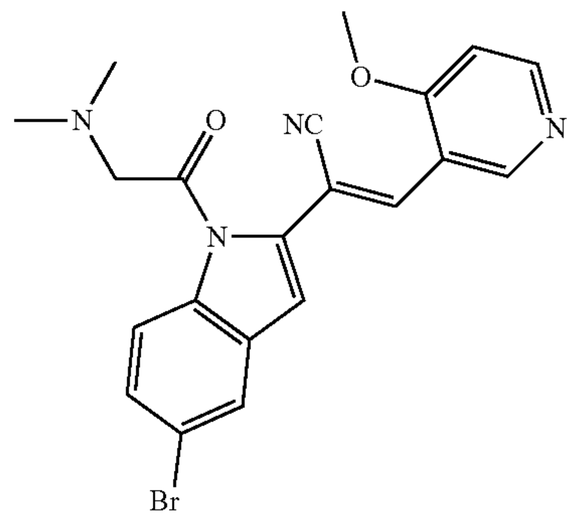
To a mixture of (Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile (50.0 mg, 1 eq) in CH_2Cl_2 was added DIPEA (0.024 mL, 1 eq) and triphosgene (64.0 mg, 0.37 eq). The mixture was stirred 20 min at room temperature and a solution of dimethylhydrazine (0.011 mL, 1 eq), DIPEA (0.024 mL, 1 eq) in CH_2Cl_2 was added. The mixture was stirred 2 h at room temperature and concentrated. The residue was purified by silicagel chromatography (CH_2Cl_2/MeOH (100:0 to 90:10) to give the title compound as a yellow solid (61%).

ESI-MS: $(M+H)^+$=440

^{1}H NMR (300 MHz, CD_3OD) δ ppm 9.00 (s, 1H), 8.53 (d, J=5.8 Hz, 1H), 8.34-8.27 (m, 1H), 8.14-8.10 (m, 2H), 7.88 (s, 1H), 7.52 (d, J=8.5 Hz, 1H), 7.25 (d, J=6.0 Hz, 1H), 4.08 (s, 3H), 2,56 (s, 6H).

Example 61

(Z)-2-(5-bromo-1-(2-(dimethylamino)acetyl)-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile



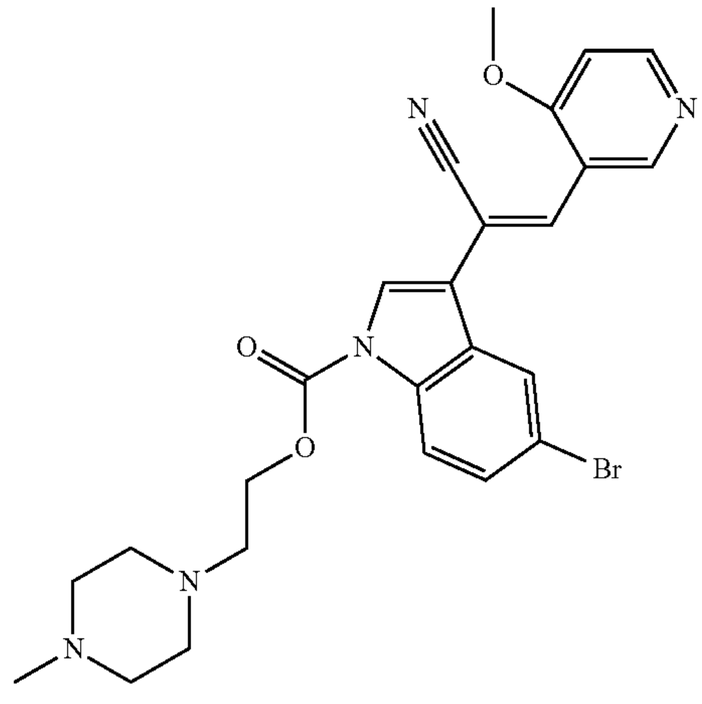
To a mixture of (Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxypyridine (60 mg) in DMF (2 ml) was added 2-(dimethylamino)acetic acid (28 mg), PyBOP (132 mg), TEA (48 μl). The mixture was stirred at RT for 2 hours, poured in water and filtered. Aspect of the pure product: yellow solid. (Yield: 87%).

APCI-MS: $(M+H)^+$=438

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 8.89 (s, 1H), 8.58 (d, J=5.8 Hz, 1H), 8.38 (d, J=8.9 Hz, 1H), 8.33 (s, 1H), 8.19 (s, 1H), 7.94 (s, 1H), 7.66 (d, J=7.3 Hz, 1H), 7.25 (d, J=5.8 Hz, 1H), 4.26 (s, 2H), 3.97 (s, 3H), 2.54 (s, 6H).

Example 62

(Z)-2-(4-methylpiperazin-1-yl)ethyl 5-bromo-3-(1-cyano-2-(4-methoxypyridin-3-yl)vinyl)-1H-indole-1-carboxylate



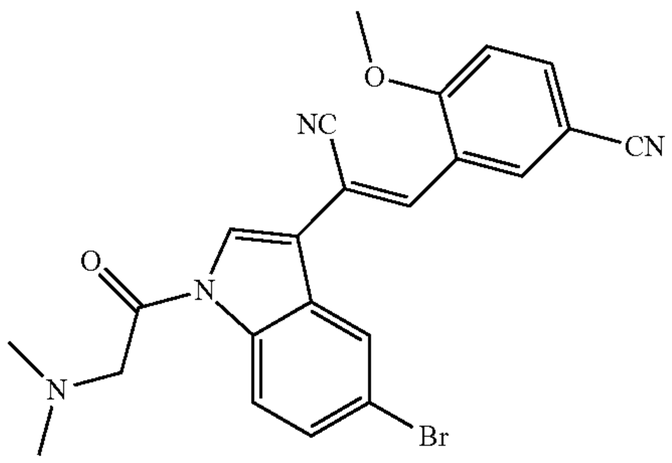
To a mixture of (Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile (30.0 mg, 1 eq) in CH_2Cl_2 (1 mL) was added NaH (7.0 mg, 1.2 eq). The mixture was stirred 10 min at room temperature and triphosgene (15.6 mg, 0.37 eq) was added. The mixture was stirred 3 h at room temperature and a solution of 2-(4-methylpiperazin-1-yl)ethanol (11.0 mg, 1 eq), DIPEA (0.024 mL, 1 eq) in CH_2Cl_2 was added. The mixture was stirred 2 h at room temperature and concentrated. The residue was purified by silicagel chromatography (CH_2Cl_2 /MeOH (100:0 to 90:10) to give the title compound as a yellow solid (41%).

ESI-MS: $(M+H)^+$=524

^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.95 (s, 1H), 8.48 (d, J=6.0 Hz, 1H), 8.07 (s, 1H), 7.73 (s, 1H), 7.69 (s, 1H), 7.48-7.29 (m, 2H), 7.21 (d, J=6.0 Hz, 1H), 4.07 (s, 3H), 3.69 (t, J=6.0 Hz), 2.74-2.40 (m, 6H), 2.29 (s, 4H).

Example 63

((Z)-3-(2-(5-bromo-1-(2-(dimethylamino)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile



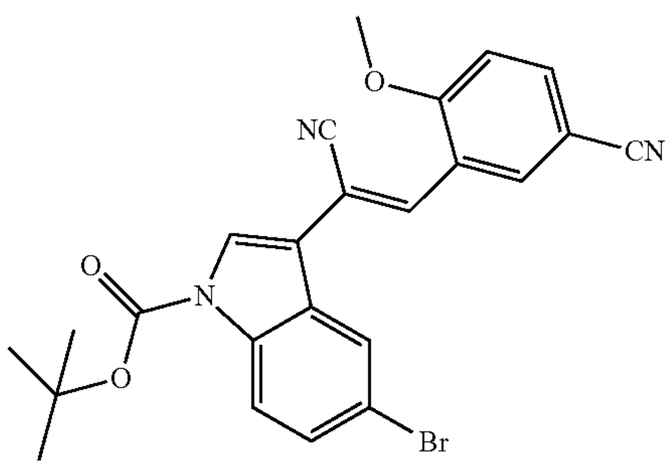
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (100 mg), DMF (2 ml), 2-(dimethylamino)acetic acid (34 mg), PyBOP (206 mg), TEA (74 µl). Reaction time 2 hours. Poured in water and diisopropylether. Aspect of the pure product: yellow solid. (Yield: 82%).

APCI-MS: (M+H)+=462

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 8.38 (d, J=10.8 Hz, 2H), 8.29 (s, 1H), 8.16 (s, 1H), 8.00 (d, J=10.7 Hz, 1H), 7.94 (s, 1H), 7.64 (d, J=10.6 Hz, 1H), 7.37 (d, J=8.8 Hz, 1H), 3.96 (d, J=10.2 Hz, 5H), 2.38 (s, 6H).

Example 64

(Z)-tert-butyl 5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indole-1-carboxylate



A mixture of (Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (150 mg), Di-tert-butyldicarbonate (104 mg), DMAP (5 mg) in acetonitrile (3 ml) was stirred at RT for 0.25 h. The mixture was poured in water and filtered. Aspect of the pure product: yellow solid. (Yield: 88%).

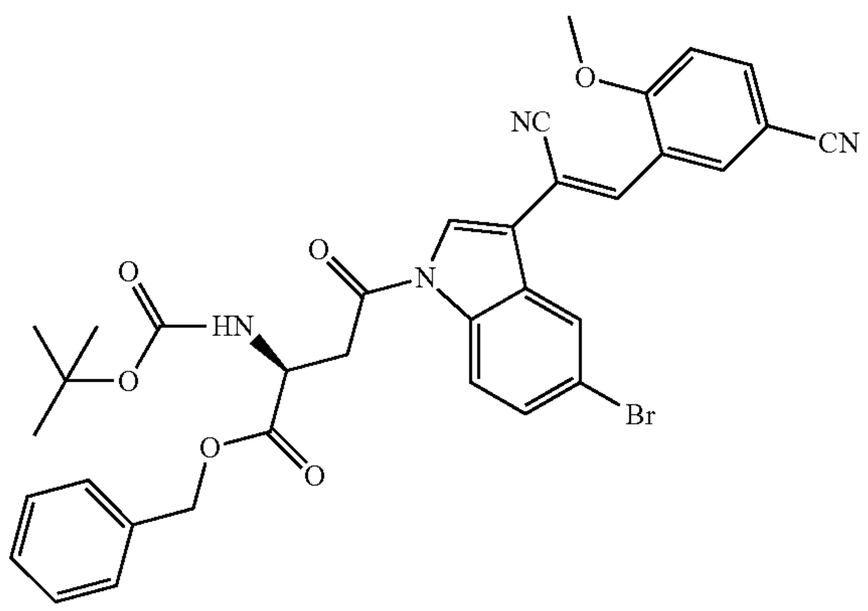
APCI-MS: (M−H−Boc)=376

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 8.26 (d, J=1.8 Hz, 1H), 8.16 (d, J=1.8 Hz, 1H), 8.11 (d, J=8.9 Hz, 1H), 8.06 (s, 1H), 8.00 (dd, J=8.7, 2.1 Hz, 1H), 7.92 (s, 1H), 7.63 (dd, J=8.9, 1.9 Hz, 1H), 7.36 (d, J=8.8 Hz, 1H), 3.97 (s, 3H), 1.65 (s, 9H).

The following examples were prepared as the previous method.

Example 65

(R,Z)-benzyl-4-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-2-(tert-butoxycarbonylamino)-4-oxobutanoate



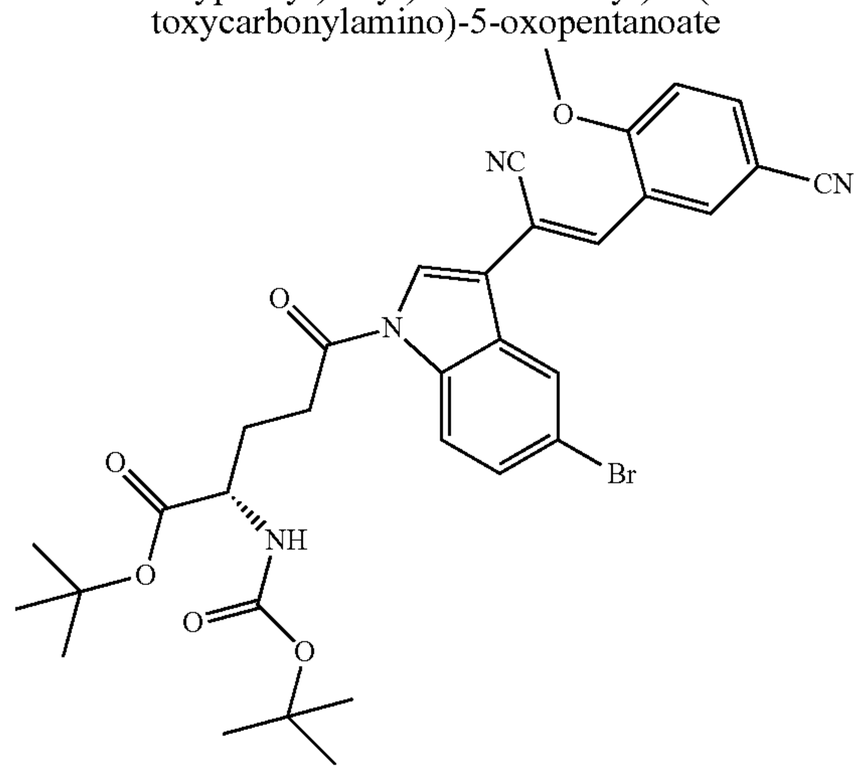
((Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (150 mg), DMF (4.5 ml), (S)-4-(benzyloxy)-3-(tert-butoxycarbonylamino)-4-oxobutanoic acid (160 mg), PyBOP (310 mg), TEA (111 µl). Reaction time 3 hours. Poured in water and diisopropylether. Aspect of the pure product: yellow solid. (Yield: 61%).

APCI-MS: (M−H−Boc)=583

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 8.37 (d, J=7.6 Hz, 2H), 8.30 (s, 1H), 8.17 (s, 1H), 8.08-7.90 (m, 2H), 7.64 (d, J=8.8 Hz, 1H), 7.46 (d, J=7.5 Hz, 1H), 7.43-7.25 (m, 6H), 5.15 (s, 2H), 4.64 (d, J=5.5 Hz, 1H), 3.98 (s, 3H), 3.60 (s, 2H), 1.36 (s, 9H).

Example 66

(R,Z)-tert-butyl-5-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-2-(tert-butoxycarbonylamino)-5-oxopentanoate



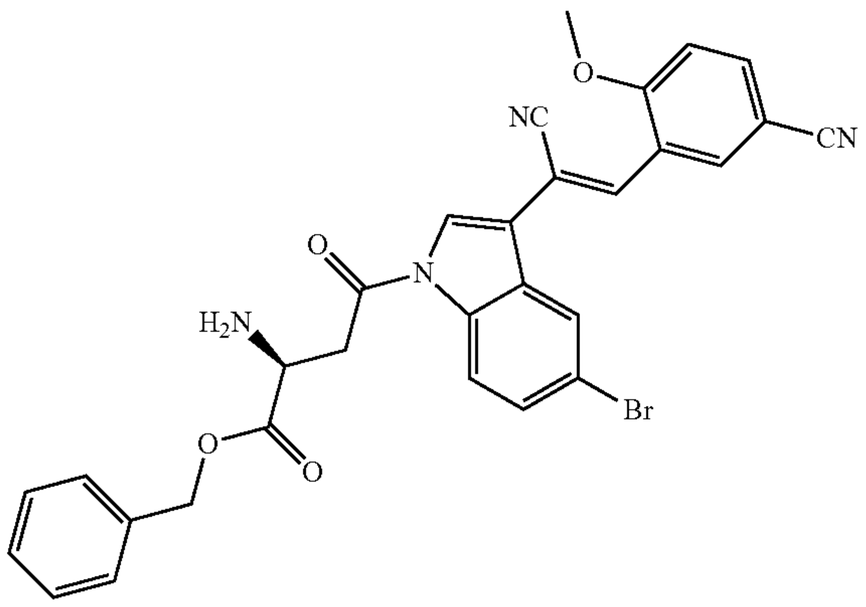
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (200 mg), DMF (5 ml), (S)-5-tert-butoxy-4-(tert-butoxycarbonylamino)-5-oxopentanoic acid (201 mg), PyBOP (413 mg), TEA (147 µl). Reaction time 2 hours. Poured in water, extracted with AcOEt and trituration of the purified product with diisopropylether. Aspect of the pure product: yellow solid. (Yield: 53%).

APCI-MS: $(M+H)^+$=507

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 8.46-8.33 (m, 2H), 8.29 (d, J=1.8 Hz, 1H), 8.17 (d, J=1.7 Hz, 1H), 8.01 (dd, J=8.7, 2.0 Hz, 1H), 7.96 (s, 1H), 7.64 (dd, J=8.9, 1.7 Hz, 1H), 7.38 (d, J=8.8 Hz, 1H), 7.22 (d, J=7.9 Hz, 1H), 3.99 (s, 4H), 3.22 (d, J=6.1 Hz, 2H), 2.13 (m, 1H), 1.99 (m, 1H), 1.39 (d, J=9.2 Hz, 18H)

Example 67

(R,Z)-benzyl-2-amino-4-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-4-oxobutanoate



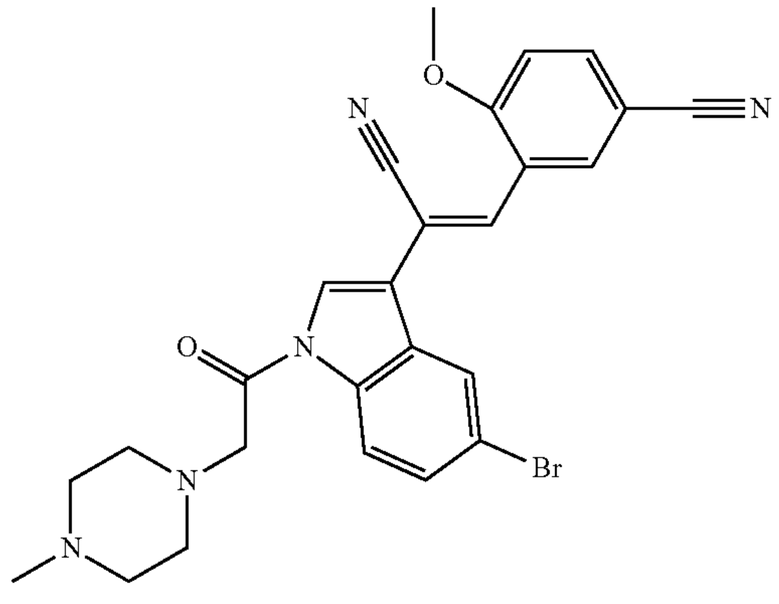
A mixture of (R,Z)-benzyl 4-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-2-(tert-butoxycarbonylamino)-4-oxobutanoate (116 mg), HCl-Dioxanne 4M (1.5 ml) in EtOH (2 ml) was stirred at RT for 24 hours. After concentration to dryness, the residue was triturated with water and filtered. Aspect of the pure product: yellow solid. (Yield: 62%).

APCI-MS: $(M+H)^+$=583

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 8.39 (s, 1H), 8.35-8.30 (m, 2H), 8.20 (d, J=1.8 Hz, 1H), 8.03 (dd, J=8.7, 2.1 Hz, 1H), 7.98 (s, 1H), 7.68 (dd, J=8.9, 1.9 Hz, 1H), 7.37 (dd, J=10.4, 6.3 Hz, 3H), 7.33-7.25 (m, 3H), 5.25 (s, 2H), 4.62 (t, J=4.9 Hz, 1H), 3.99 (s, 3H), 3.86 (d, J=3.9 Hz, 2H)

Example 68

(Z)-3-(2-(5-bromo-1-(2-(4-methylpiperazin-1-ypacetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile



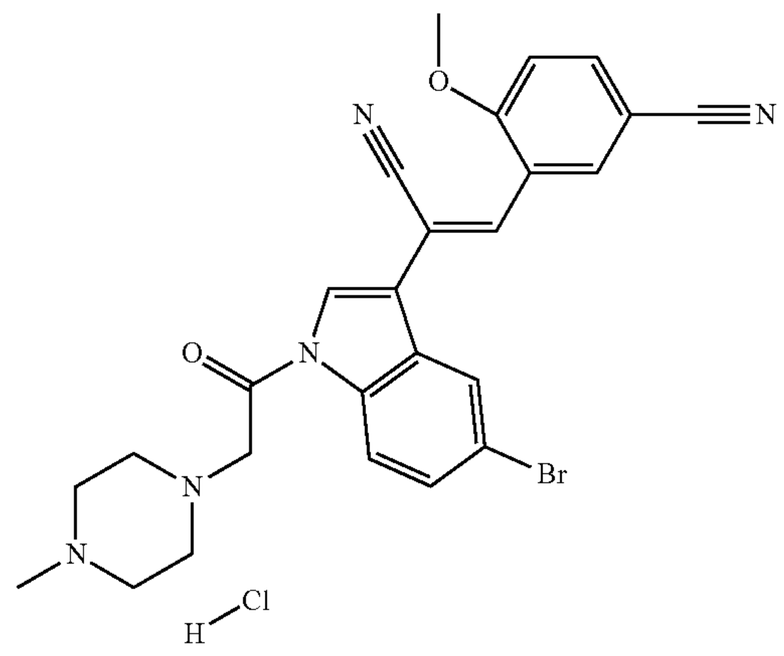
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (150 mg), 2-(4-methylpiperazin-1-yl) acetic acid (78 mg), PyBOP (310 mg), Triethylamine (0.11 ml), DMF (2 ml). Reaction time 5 h at RT. Poured in water and tritured with methylene chloride. Aspect of the product: yellow solid. (Yield: 92%)

APCI-MS: $(M+H)^+$=518

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 8.43-8.32 (m, 2H), 8.30 (d, J=1.8 Hz, 1H), 8.19 (d, J=1.7 Hz, 1H), 8.02 (dd, J=8.8, 2.0 Hz, 1H), 7.95 (s, 1H), 7.65 (dd, J=8.9, 1.8 Hz, 1H), 7.38 (d, J=8.8 Hz, 1H), 4.13 (s, 2H), 3.98 (s, 3H), 2.97 (m, 8H), 2.68 (s, 3H).

Example 69

(Z)-3-(2-(5-bromo-1-(2-(4-methylpiperazin-1-yl) acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride



A suspension of (Z)-3-(2-(5-bromo-1-(2-(4-methylpiperazin-1-yl)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (114 mg), HCl-Dioxane 4M (0.3 ml) in dioxane (1 ml) was stirred few minutes and concentrated under vacuum. Aspect of the product: yellow solid. (Yield: 95%)

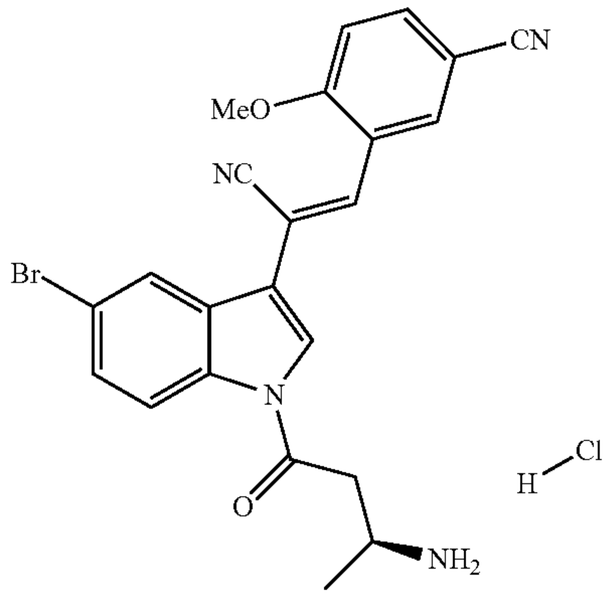
APCI-MS: $(M+H)^+$=518

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 10.47 (s, 1H), 8.43-8.33 (m, 2H), 8.30 (d, J=1.8 Hz, 1H), 8.19 (d, J=1.8 Hz, 1H), 8.02 (dd, J=8.7, 2.1 Hz, 1H), 7.96 (s, 1H), 7.66 (dd, J=8.9, 1.9 Hz, 1H), 7.39 (d, J=8.8 Hz, 1H), 4.33 (s, 2H), 3.98 (s, 3H), 3.44 (d, J=11.5 Hz, 2H), 3.19 (s, 4H), 2.91 (s, 2H), 2.78 (s, 3H).

The following examples were prepared as the previous method

Example 70

(S,Z)-3-(2-(1-(3-aminobutanoyl)-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride



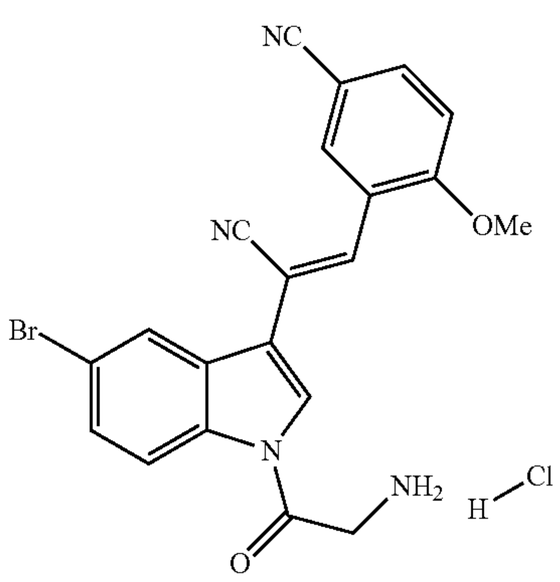
(S,Z)-tert-butyl 4-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-4-oxobutan-2-ylcarbamate (125 mg), HCl 37% (0.092 ml), EtOH (2 ml). Reaction time 1 h at reflux. Aspect of the pure product: yellow solid. (Yield: 65%).

APCI-MS: $(M+H)^+$=463

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 8.44-8.34 (m, 2H), 8.29 (d, J=1.9 Hz, 1H), 8.19 (d, J=1.8 Hz, 1H), 8.13-7.82 (m, 5H), 7.66 (dd, J=8.9, 1.9 Hz, 1H), 7.37 (d, J=8.8 Hz, 1H), 3.97 (s, 3H), 3.76 (dd, J=13.0, 6.4 Hz, 1H), 3.53-3.42 (m, 2H), 1.34 (d, J=6.6 Hz, 3H).

Example 71

(Z)-3-(2-(1-(2-aminoacetyl)-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride



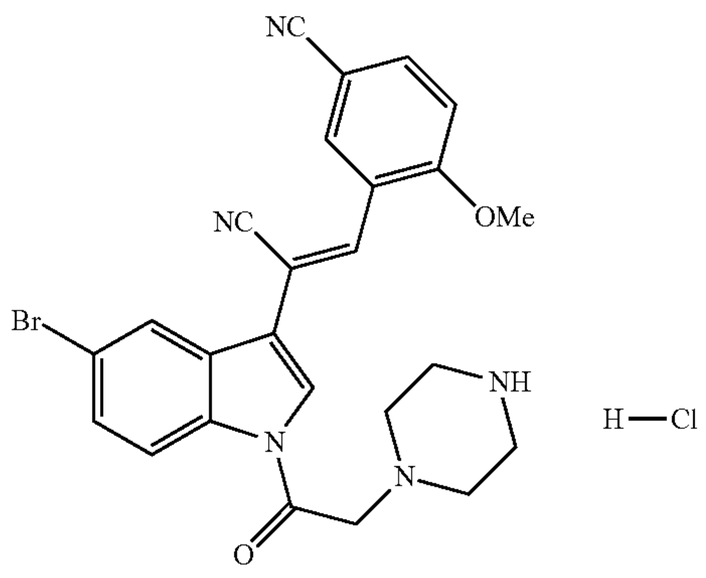
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (150 mg), 2-(tert-butoxycarbonylamino)acetic acid (87 mg), PyBOP (310 mg), Triethylamine (0.11 ml), Reaction time 3 hours at RT. Then HCl 37% (0165 ml), DMF (2 ml) 2 hours at reflux. Aspect of the product: yellow solid. (Yield: 50%)

APCI-MS: $(M+H)^+$=435

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 8.60 (s, 2H), 8.38 (d, J=8.4 Hz, 2H), 8.31 (d, J=1.9 Hz, 1H), 8.22 (d, J=1.8 Hz, 1H), 8.06-7.97 (m, 2H), 7.70 (dd, J=8.9, 1.9 Hz, 1H), 7.39 (d, J=8.8 Hz, 1H), 4.68 (s, 2H), 3.98 (s, 3H).

Example 72

(Z)-3-(2-(5-bromo-1-(2-(piperazin-1-yl)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride



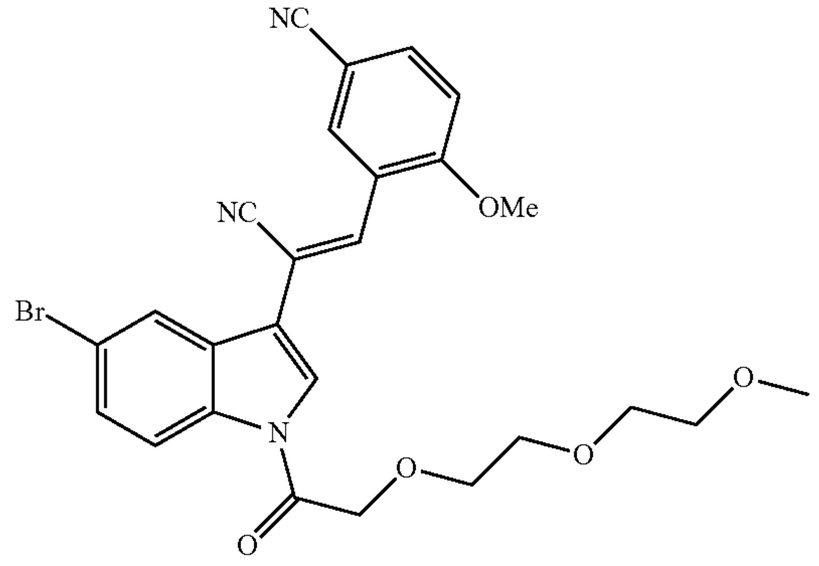
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (150 mg), 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)acetic acid (121 mg), PyBOP (310 mg), Triethylamine (011 ml), reaction time 3 hours at RT. Then HCl 37% (0.165 ml), DMF (2 ml) 2 hours at reflux. Aspect of the product: yellow solid. (Yield: 46%)

APCI-MS: $(M+H)^+$=504

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 9.36 (s, 1H), 8.44-8.33 (m, 2H), 8.31 (d, J=1.8 Hz, 1H), 8.21 (d, J=1.8 Hz, 1H), 8.03 (dd, J=8.7, 2.1 Hz, 1H), 7.96 (s, 1H), 7.68 (dd, J=8.9, 1.8 Hz, 1H), 7.39 (d, J=8.8 Hz, 1H), 4.62 (s, 2H), 3.98 (s, 3H), 3.26 (d, J=17.6 Hz, 8H).

Example 73

(Z)-3-(2-(5-bromo-1-(2-(2-(2-methoxyethoxy)ethoxy)acetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile



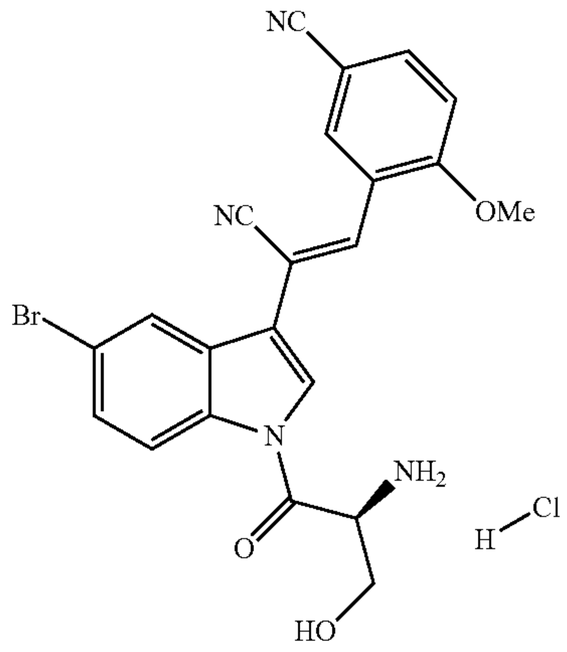
(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (150 mg), 2-(2-(2-methoxyethoxy)ethoxy)acetic acid (88 mg), PyBOP (310 mg), Triethylamine (0.11 ml), DMF (2 ml). Reaction time 18 hours at RT. Poured in water and washed with acetonitrile. Aspect of the product: yellow solid. (Yield: 33%)

APCI-MS: $(M+H)^+$=538

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 8.39 (d, J=8.9 Hz, 1H), 8.33-8.23 (m, 2H), 8.18 (d, J=1.7 Hz, 1H), 8.01 (dd, J=8.7, 2.0 Hz, 1H), 7.94 (s, 1H), 7.65 (dd, J=8.9, 1.8 Hz, 1H), 7.38 (d, J=8.8 Hz, 1H), 4.93 (s, 2H), 3.98 (s, 3H), 3.81-3.68 (m, 2H), 3.60 (d, J=5.0 Hz, 2H), 3.55-3.48 (m, 2H), 3.39 (d, J=5.3 Hz, 2H), 3.19 (s, 3H).

Example 74

(S,Z)-3-(2-(1-(2-amino-3-hydroxypropanoyl)-5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile hydrochloride



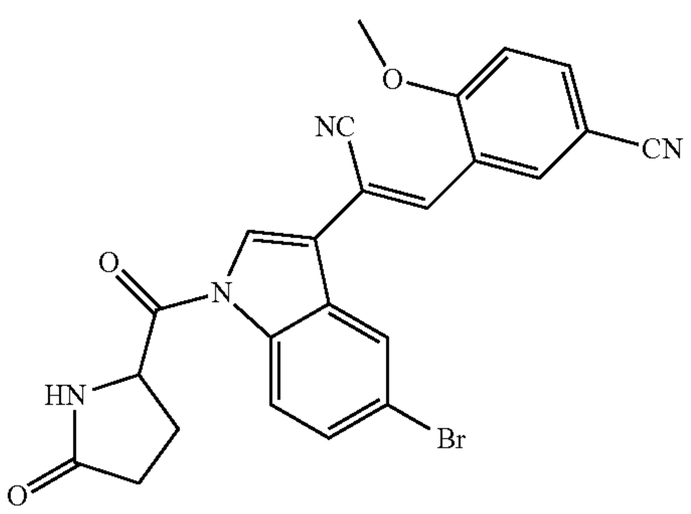
(S,Z)-tert-butyl 1-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-3-hydroxy-1-oxopropan-2-ylcarbamate (220 mg), HCl 37% (110 μl), EtOH (2 ml). Reaction time 1 h at reflux. Aspect of the product: yellow solid. (Yield: 61%).

APCI-MS: $(M+H)^+$=465

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 8.68 (d, J=19.5 Hz, 3H), 8.38 (d, J=8.9 Hz, 1H), 8.31 (d, J=1.9 Hz, 1H), 8.20 (d, J=1.8 Hz, 1H), 8.01 (dd, J=9.6, 2.9 Hz, 2H), 7.70 (dd, J=8.9, 1.9 Hz, 1H), 7.38 (d, J=8.8 Hz, 1H), 5.69 (s, 1H), 5.24 (s, 1H), 3.96 (d, J=5.0 Hz, 5H).

Example 75

(Z)-3-(2-(5-bromo-1-(5-oxopyrrolidine-2-carbonyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile



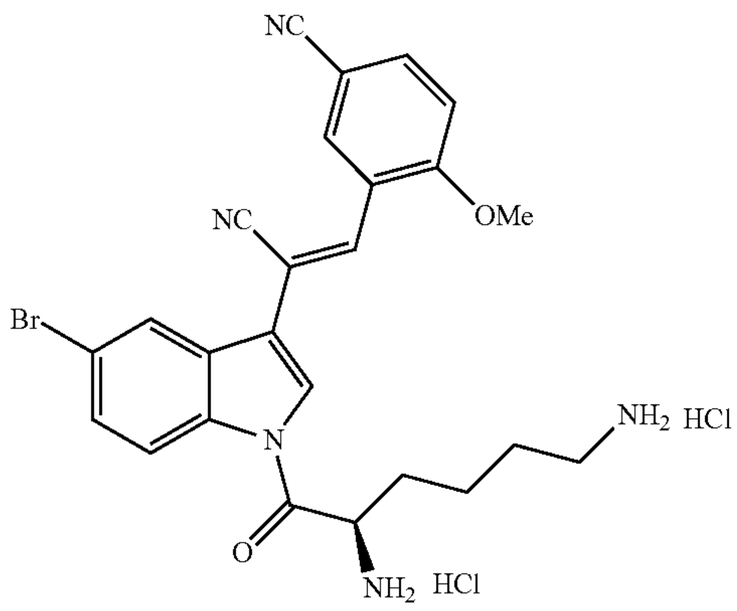
To a mixture of (Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (100 mg) in DMF (2 ml) was added 5-oxopyrrolidine-2-carboxylic acid (37 mg), BOP (128 mg), TEA (58 μl). The mixture was stirred at RT for 3 hours, poured in water and filtered. Aspect of the pure product: yellow solid. (Yield: 60%).

ESI+MS: $(M+H)^+$=490

^{1}H NMR (300 MHz, MeOD-d6) δ ppm 8.44 (s, 1H), 8.22 (s, 1H), 8.08 (s, 1H), 7.91 (dd, J=8.8, 2.0 Hz, 1H), 7.95 (s, 1H), 7.65 (dd, J=14.0, 2.1 Hz, 2H), 7.71 (s, 1H), 7.40-7.31 (m, 2H), 4.21 (t, J=6.0 Hz, 1H), 3.98 (s, 3H), 2.73-2.13 (m, 4H).

Example 76

(R,Z)-3-(2-(5-bromo-1-(2,6-diaminohexanoyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile dihydrochloride



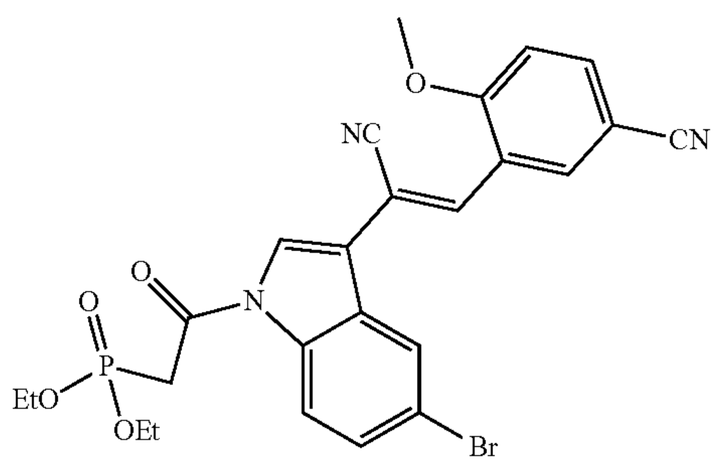
(R,Z)-tert-butyl-6-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-6-oxohexane-1,5-diyldicarbamate (320 mg), HCl 37% (164 μl), EtOH (3 ml). Reaction time 1 hour at reflux. Aspect of the pure product: pale yellow solid. (Yield: 67%)

APCI-MS: $(M+H)^+$=506

^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.68 (s, 3H), 8.40 (d, J=8.9 Hz, 1H), 8.32 (d, J=1.7 Hz, 1H), 8.22 (d, J=1.8 Hz, 1H), 8.07-8.00 (m, 2H), 7.91 (s, 2H), 7.71 (dd, J=8.9, 1.8 Hz, 1H), 7.40 (d, J=8.8 Hz, 1H), 5.19 (s, 1H), 3.99 (s, 3H), 2.72 (s, 2H), 1.96 (s, 2H), 1.46 (m, 4H).

Example 77

(Z)-diethyl (2-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-2-oxoethyl) phosphonate



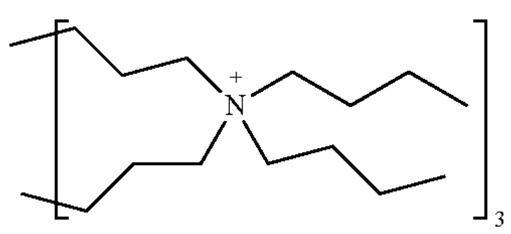
To a solution of (Z)-2-(5-chloro-1H-indol-3-yl)-3-(4-methoxypyridin-3-yl)acrylonitrile (0.382 g, 1 eq) in THF (6 mL) was added NaH 60% in mineral oil (0.048 g, 1.2 eq). The resulting solution was stirred 30 min at room temperature and a solution of diethyl(2-chloro-2-oxoethyl)phosphonate (0.216 g, 1 eq) in THF (3 mL). The mixture was stirred overnight, quenched with saturated NH_4Cl, extracted with AcOEt, dried over Na_2SO_4, filtrated and concentrated. The residue was purified by silicagel chromatography CH_2Cl_2/MeOH (100:0 to 90:10) to give the title compound as yellow solid (36%).

ESI-MS: $(M+H)^+$=556

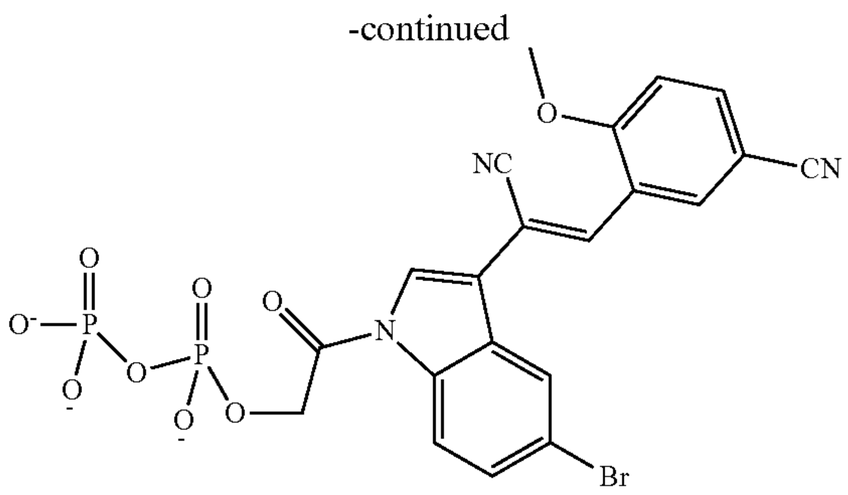
^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.28 (s, 1H), 8.07 (s, 1H), 7.81 (dd, J=8.5 Hz, 1.8 Hz, 1H), 7.43 (d, J=8.9 Hz, 1H), 7.36 (d, J=8.9 Hz, 1H), 7.29 (d, J=8.5 Hz, 1H), 4.2 (q, J=7.0 Hz, 4H), 4.06 (s, 3H), 3.10 (d, J=20.0 Hz, 2H), 1.36 (t, J=7.0 Hz, 6 H).

Example 78

(Z)-2-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-2-oxoethyl diphosphate, tetrabutylammonium salt



-continued



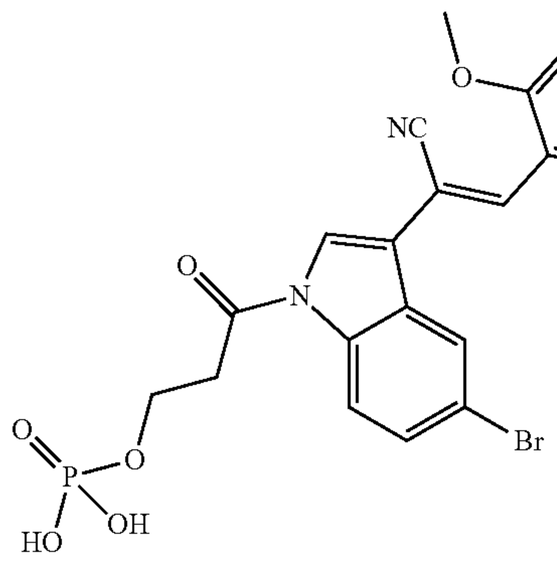
To a solution of (Z)-3-(2-(5-bromo-1-(2-bromoacetyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (0.036 g, 1 eq) in AcCN (1 mL) was added Tributylammonium pyrophosphate (0.092 g, 1.3 eq). The reaction mixture was stirred 48 h at room temperature and concentrated to give the title compound as a yellow solid (60%).

ESI-MS: $(M-H)^+$=590

^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.24 (d, J=1.9 Hz, 1H), 8.00 (s, 1H), 7.75 (dd, J=8.7 Hz, 2.1 Hz, 1H), 7.71-7.67 (m, 2H), 7.50 (d, J=8.7 Hz, 1H), 7.35 (s, 1H), 7. 31 (dd, J=8.7 Hz, 1.7 Hz, 1H), 7.25 (d, J=8.7 Hz, 1H), 4. 97 (d, J=20 Hz, 2H), 4.03 (s, 3H), 4.06 (s, 3H), 3.27-3,22 (m, 24 H), 1.72-1.62 (m, 24 H), 1.49-1.37 (m, 24 H), 1.03 (t, J=7. 2 Hz, 36 H).

Example 79

(Z)-3-(5-bromo-3-(1-cyano-2-(5-cyano-2-methoxyphenyl)vinyl)-1H-indol-1-yl)-3-oxopropyl dihydrogen phosphate



To a solution of (Z)-3-(2-(5-bromo-1-(3-hydroxypropanoyl)-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile (0.047 g, 1 eq) in THF (3.1 mL) and AcCN (3.6 mL) was added DIPEA (90 υL). The reaction mixture was cooled to 0° C. and $POCl_3$ (0.078 mL, 8 eq) was added dropwise. The resulting solution was stirred 3 h at 0° C. and 1 M KH_2PO_4 (PH=4) (5 mL) was added dropwise. The mixture was stirred overnight and concentrated. The residue was purified by C18 flash chromatography H_2O/MeOH (100:0 to 0:100) to give the title compound as yellow solid (40%).

^{1}H NMR (300 MHz, CD_3OD) δ ppm 8.30 (s, 1H), 8.04 (s, 1H), 8.00-7.97 (m, 2H), 7.83-7.80 (m, 2H), 7.40 (dd, J=9.0 Hz, 1.5 Hz, 1H), 7.29 (d, J=8.7 Hz, 1H), 4.06 (s, 3H), 3.73 (m, 2 H), 3.23 (m, 2H).

Evaluation of Inhibitory Effects on the Microtubule Stimulated ATPase Activity of the MKlp2 Motor Domain.

Material and Methods

MKlp2 ATPase activity was measured by monitoring real time free phosphate generation using the Kinesin ELIPA Assay Kit. The assay is based upon an absorbance shift (330 nm-360 nm) that occurs when 2-amino-6-mercapto-7-methylpurine ribonucleoside (MESG) is catalytically converted to 2-amino-6-mercapto-7-methylpurine in the presence of inorganic phosphate (Pi). One molecule of Pi will yield one molecule of 2-amino-6-mercapto-7-methylpurine in an essentially irreversible reaction. Hence, the absorbance at 360 nm is directly proportional to the amount of Pi generated in the kinesin ATPase reaction. Human recombinant MKlp2 motor domain$_{I\text{-}519}$, His tagged (Cytoskeleton, Cat. #MP05), plus porcine brain microtubules (Cytoskeleton, cat. #MT002) were used.

All experiments were performed at 22° C.

Condition 1, Compound Preparation.

The compounds were disolved in DMSO at 30× the maximum concentration to be tested. Each compound had a seven point dose-response evaluation, with final concentrations 100, 33, 11, 3.7, 1.2, 0.4, 0.13 μM. DMSO solutions were pipetted directly into each well.

Condition 2, Reaction's "Motor Mix".

The following were mixed sequentially in the specified order at RT to obtain the "motor mix".

20 mL: 15 mM Pipes-NaOH pH 7.0, 10 mM $MgCl_2$, 30 μM Tx (Buffer 1).

10 mL: 5× MSEG (ELIPA 1 reagent, Cat. #BK051).

10 mL: 2.5 mg/mL porcine brain microtubules (3×10 mg Cat. #MT002-XL resuspended in 12 mL of Buffer 1).

0.25 mL: 500 μg/mL MKlp2 protein.

0.5 mL: 100× PNP (ELIPA 2 reagent, cat. #BK051).

Condition 3, Reaction Initiation.

The motor mix was pipetted into each well to obtain 80% of total volume. The reaction was initiated by adding a 20% of total volume of 5 mM ATP into each well.

The reactions were measured in a SpectraMax M2 (Molecular Devices) set in kinetic mode and 360 nm absorbance wavelength. The start protocol was 5 second rapid circular mixing, 21 readings, 30 seconds apart.

IC50 values were determined as the concentration to inhibit 50% of the MKlp2 ATPase activity.

Evaluation of Cytotoxicity Effects on Human Cancer Cells

Material and Methods

The effects of the compounds of the invention on the viability of human cancer cells were studied on various human cancer cell lines of differing tissue origins (A549, NCI-H460: lung cancer; MDA-MB-231: breast cancer; HCT-116, HT-29: colon cancer; MIA-PaCa-2: pancreatic cancer; K562: leukaemia). All cell lines were obtained from ATCC or ECACC.

Cells were cultured in the culture media described below, under a 37° C., 5% CO_2 humidified atmosphere, according to a standard operating procedure.

Organ Cell Line Culture Medium

A549: RPMI 1640+10% FBS+2 mM sodium pyruvate

NCI-H460: RPMI 1640+10% FBS+10 mM HEPES+1 mM Sodium pyruvate+2.5 g/l glucose

HCT-116: Mc Coy's 5a+10% FBS+0.5 mM Ultraglutamine

HT-29: Mc Coy's 5a+10% FBS+0.5 mM Ultraglutamine

MDA-MB-231: Ham's F12+10% FBS

K562: RPMI 1640+10% FBS+2 mM ultraglutamine

MIA-PaCa-2: DMEM+10% FBS

On D0, the cells were plated in 90 μl in 96 wells plates at densities ranging from 500 to 5,000 cells per well.

On D1, the cells were treated as described below: the compounds of invention were diluted in DMSO in order to obtain a concentration of 5 mM. This solution was serially diluted in PBS+10% FBS in order to obtain the concentrations of 500.000, 166.667, 55.555, 18.518, 6.173, 2.058, 0.686, 0.229, 0.076 and 0.025 μM. The addition of 10 μl in each well allowed the testing concentrations of 50.000, 16.6667, 5.5555, 1.8518, 0.6173, 0.2058, 0.0686, 0.0229, 0.0076 and 0.0025 μM.

Following addition of the test substance the cells were protected from light. The solvents (DMSO and specific control solvent were added at the maximal concentration: 10 μl/well (3 wells/condition)).

On D4, the Cell Proliferation Reagent WST-1 was added to each well (10 μl/well), according to a standard operating procedure. The cells were then incubated for 30 min to 4 h at 37° C.-5% CO_2. After these incubations, the 96-well plates were shaken thoroughly for 1 min with Multiskan® EX apparatus (Thermo Labsystems, France). The absorbence was measured at 450 nm, the reference wavelength being 620 nm. The analysis of the results was performed with the Ascent software 2.6 (ThermoLabsystems, France), Microsoft Excel 2003 and GraphPad Prism 4.03 softwares to give the concentration of the compounds that induces the death of 50% of the cells (IC50).

The results for some compounds considered in above-cited examples in term of inhibition of microtubule stimulated ATPase activity of MKlp2 are illustrated in Tables 3 and 6 hereafter.

The results for some compounds considered in above-cited examples in term of cytotoxicity on K562 cells are illustrated in Table 4 and 6 hereafter.

The results for some compounds considered in above-cited examples in term of cytotoxicity on other human cancer cells are illustrated in Table 5 hereafter.

TABLE 3

	X	R1	R1'	R2	R3	MKIp2 IC50 (μM)
W02010/150211-Example 1	N	H	H	H	H	3.8
W02010/150211-Example 4	N	—O—CH_3	H	H	H	4.2
W02010/150211-Example 22	N	—O—CH_2—CH_3	H	H	H	5.2
W02010/150211-Example 23	N	—O—CH—$(CH_3)_2$	H	H	H	5.2
W02010/150211-Example 24	N	—Cl	H	H	H	1.1
W02010/150211-Example 28	N	—O—CH_3	H	H	—F	2.4
W02010/150211-Example 31	N	—O—CH_3	H	—CH_3	H	2.3
W02010/150211-Example 47	N	—O—CH_3	H	—Cl	H	1.6
W02010/150211-Example 37	N	—Br	H	H	H	1.5
W02010/150211-Example 26	N	H	—O—CH_3	H	H	26.5
W02010/150211-Example 52	N	—O—CH_3	H	H	—O—CH_3	12.6
W02010/150211-Example 30	C—CN	—O—CH_3	H	H	H	4.4
Example 2	N	—O—CH_3	H	—O—CH_2—CH_3	H	0.3
Example 3	N	—Cl	H	—Cl	H	0.8
Example 4	N	—Br	H	—Cl	H	0.7
Example 5	N	—Br	H	—O—CH_3	H	0.05
Example 5b	N	—Br	H	—O—CH_3	H	0.61
Example 6	N	—Cl	H	—N—$(CH_3)_2$	H	0.5
Example 7	N	—Cl	H	—N—$(CH_3)_2$	H	0.8
Example 8	N	—Br	H	—N—$(CH3)_2$	H	0.9
Example 9	N	—Cl	H	—O—CH_3	H	0.1
Example 10	N	—Cl	H	—O—C_6H_5	H	0.3
Example 11	N	—Br	H	—O—C_6H_5	H	0.5
Example 12	N	—O—CH_3	H	—O—CH_3	H	0.3
Example 13	N	—Br	H	—O—CH_2—CH_3	H	0.1
Example 14	N	—Br	H	—O—CH—$(CH_3)_2$	H	0.2
Example 15	N	—Br	H	—S—CH_3	H	0.2
Example 16	N	—Br	H	—S—CH_2—CH_3	H	0.3
Example 17	N	—Br	H	—(C_6H_4)-3-Br	H	0.3
Example 18	N	—Cl	H	—(C_6H_4)-3-Br	H	0.3
Example 19	N	—Br	H	—S—C_6H_5	H	0.3
Example 20	N	—Br	H	—S—CH_2—C_6H_5	H	0.2
Example 21	N	—Br	H	—S—C_6H_5-3,4-(—$OCH_3)_2$	H	0.4
Example 22	N	—Br	H	—O—C_6H_5-4-F	H	0.09
Example 23	N	—Cl	H	—O—C_6H_5-4-F	H	0.09
Example 24	N	—Br	H	—N—$(CH_2CH_3)_2$	H	1.1
Example 25	N	—Br	H	—C_6H_5-4-CF_3	H	0.4
Example 26	N	—Cl	H	—C_6H_5-4-CF_3	H	0.5
Example 27	N	—Cl	H	—S—C_6H_5-4-F	H	0.3
Example 28	N	—Br	H	—S—C_6H_5-4-F	H	0.09
Example 29	N	—Cl	H	—C_4H_3O	H	0.03
Example 30	N	—Cl	H	—S—C_5H_4N	H	0.3
Example 31	N	—Br	H	—S—C_5H_4N	H	0.4
Example 32	N	—Br	H	—$C_2H_2N_3$	H	0.06
Example 33	N	—Cl	H	—$C_2H_2N_3$	H	0.1
Example 34	N	—Br	H	—C_4H_3O	H	0.07
Example 34b	N	—Br	H	—C_4H_3O	H	0.96
Example 35	N	—Cl	H	—O—CH_3	H	<0.07
Example 36	N	—Br	H	—S—$(CH_2)_2$—N—$(CH_3)_2$	H	0.3
Example 37	C—CN	—Br	H	—O—C_6H_5-4-F	H	0.9
Example 38	C—CN	—Br	H	—O—CH_3	H	0.2
Example 39	C—CN	—Br	H	—N—$(CH_3)_2$	H	0.2
Example 40	C—CN	—Cl	H	—O—CH_3	H	0.2

TABLE 3-continued

	X	R1	R1'	R2	R3	MKIp2 IC50 (μM)
Example 41	C—CN	—Cl	H	—N—$(CH_3)_2$	H	0.4
Example 42	C—CN	—Cl	H	—S—CH_2CH_3	H	0.6
Example 45	N	H	—Br	—O—CH_3	H	0.2
Example 46	N	H	—F	—O—CH_3	H	0.12
Example 47	N	H	—Cl	—O—CH_3	H	0.2
Example 48	N^+—O^-	—Br	H	—C_4H_3O	H	0.73
Example 49	N^+—O^-	—Cl	H	—O—CH_3	H	0.56
Example 54	C—CN	H	O—CH_3	—O—CH_3	H	1.4
Example 59: Prodrug with Ra = $COCH_2CO_2CH_3$	N	Br	H	—O—CH_3	H	0.57
Example 62: Prodrug with Ra = $CO_2(CH_2)$2-piperazinyl-CH_3	N	Br	H	—O—CH_3	H	0.35

TABLE 4

	X	R1	R1'	R2	R3	K562 IC50 (μM)
W02010/150211-Example 1	N	H	H	H	H	21.4
Example 3	N	—Cl	H	—Cl	H	3.6
Example 4	N	—Br	H	—Cl	H	1.4
Example 5	N	—Br	H	—O—CH_3	H	0.8
Example 5b	N	—Br	H	—O—CH_3	H	3.92
Example 34b	N	—Br	H	—C_4H_3O	H	14.26
Example 8	N	—Br	H	—N—$(CH3)_2$	H	7.5
Example 9	N	—Cl	H	—O—CH_3	H	1.4
Example 12	N	—O—CH_3	H	—O—CH_3	H	0.9
Example 15	N	—Br	H	—S—CH_3	H	2.9
Example 24	N	—Br	H	—N—$(CH_2CH_3)_2$	H	3.1
Example 29	N	—Cl	H	—C_4H_3O	H	4.7
Example 34	N	—Br	H	—C_4H_3O	H	2.2
Example 38	C—CN	—Br	H	—O—CH_3	H	0.03
Example 39	C—CN	—Br	H	—N—$(CH_3)_2$	H	0.6
Example 48	N^+—O^-	—Br	H	—C_4H_3O	H	6.71
Example 49	N^+—O^-	—Cl	H	—O—CH_3	H	9.23
Example 50	N	Cl	H	—OH	H	14.72
Example 51	C—CN	Br	H	—OH	H	0.5
Example 52	C—CN	Cl	H	—OCF_3	H	0.85
Example 53	C—CN	Br	H	—OCF_3	H	0.38
Example 54	C—CN	H	—O—CH_3	—O—CH_3	H	0.02

TABLE 5

	X	R1	R1'	R2	R3	IC50 (μM)
Example 5	N	—Br	H	—O—CH_3	H	HCT-116: 0.7 MDA-MB-231: 1.7 MIA-PaCa-2: 0.7 NCIH460: 0.9
Example 38	C—CN	—Br	H	—O—CH_3	H	HCT-116: 0.06 MDA-MB-231: 0.07

TABLE 5-continued

	X	R1	R1'	R2	R3	IC50 (μM)
Example 39	C—CN	—Br	H	—N—$(CH_3)_2$	H	MIA-PaCa-2: 0.04 NCIH460: 0.04 A549: 0.5 HT-29: 0.3 MDA-MB-231: 0.3 MIA-PaCa-2: 0.2

TABLE 6

	X	R1	R1'	R2	R3	Z/E	Ra	MKIp2 IC50 (μM)	K562 IC50 (μM)
Example 55	N	Br	H	OCH_3	H	Z	$COCH_3$	13.7	0.55
Example 56	C—CN	Br	H	OCH_3	H	Z	$COCH_3$	16.7	0.25
Example 57	N	Br	H	OCH_3	H	Z	$COC(CH_3)_3$	20	0.2
Example 58	C—CN	Br	H	OCH_3	H	Z	$COC(CH_3)_3$	7.5	0.06
Example 61	N	Br	H	OCH_3	H	Z	$COCH_2N(CH_3)_2$	0.4	0.33
Example 63	C—CN	Br	H	OCH_3	H	Z	$COCH_2N(CH_3)_2$	10.6	0.04
Example 64	C—CN	Br	H	OCH_3	H	Z	$CO_2C(CH_3)_3$	19.6	0.24
Example 65	C—CN	Br	H	OCH_3	H	Z	$COCH_2$—CH(NHBoc)Cbz	10.1	0.04

TABLE 6-continued

	X	R1	R1'	R2	R3	Z/E	Ra	MKIp2 IC50 (μM)	K562 IC50 (μM)
Example 66	C—CN	Br	H	OCH_3	H	Z	$CO(CH_2)_2$—CH(Boc)—NHBoc	5.4	0.03
Example 67	C—CN	Br	H	OCH_3	H	Z	$COCH_2$—$CH(NH_2)$—Cbz	3.1	0.04
Example 68	C—CN	Br	H	OCH_3	H	Z	CO—CH_2-piperazinyl-CH_3	>50	0.03
Example 69	C—CN	Br	H	OCH_3	H	Z	CO—CH_2-piperazinyl-CH_3•HCl	>50	0.03
Example 70	C—CN	Br	H	OCH_3	H	Z	$COCH_2$—$CH(CH_3)NH_2$	>50	0.01
Example 71	C—CN	Br	H	OCH_3	H	Z	$COCH_2NH_2$•HCl	1.9	0.01
Example 72	C—CN	Br	H	OCH_3	H	Z	CO—CH_2-piperazinyl•HCl	>50	0.01
Example 73	C—CN	Br	H	OCH_3	H	Z	$COCH_2O(CH_2)_2O(CH_2)_2OCH_3$	>50	0.03
Example 74	C—CN	Br	H	OCH_3	H	Z	$COCH(NH_2)CH_2OH$	2.1	0.01
Example 75	C—CN	Br	H	OCH_3	H	Z	CO-oxopyrrolidine	4.6	0.02
Exemple 76	C—CN	Br	H	OCH_3	H	Z	$COCH(NH_2)$—$(CH_2)_4NH_2$	1.3	0.04
Exemple 79	C—CN	Br	H	OCH_3	H	Z	$CO(CH_2)_2PO_4H_2$	>50	0.4

Stability Studies in Mouse or Human Plasma

The study was to evaluate the stability of the disclosed compounds after incubation in mouse or human plasma and to measure the metabolites formed. For the disclosed compound, a stock solution was prepared at 200 μM in DMSO. This solution was then 100-fold diluted in 1 ml of mouse or human plasma in order to obtain the required concentration of 2 μM. One aliquot of 100 μl was taken (T0) and the remaining solution was incubated at 37° C. in water bath for 60 min, 120 min and 240 min.

At the end of each incubation time 100 μl of plasma was taken, 100 μl of acetonitrile containing 0.1% of formic acid were added to each aliquot in order to stop the enzymatic reaction and to precipitate the proteins. Samples was vortexed/mixed and centrifuged 5 min at 16434.6 g (=14000 rpm) (4° C.). After centrifugation, the clear supernatant (at least 150 μl) was transferred into 1.2 ml HPLC glass vials and sealed. Samples were placed into the refrigerated autosampler and 20 μl were injected into a HPLC-MS/MS.

The Results are expressed with the percentage of test substance remaining by comparing area under specific chromatographic peak of test samples after incubation with area under specific chromatographic peak at T0 (Tables 7 and 8 and FIGS. **1** and **2**).

TABLE 7

Incubation time (min)	Remaining compound 63 (%) (mean ± SEM, n = 2) Mouse plasma	Human plasma
0	100.0 ± 0.0	100.0 ± 0.0
60	9.0 ± 0.8	49.2 ± 5.1
120	10.7 ± 8.7	27.2 ± 5.4
240	4.9 ± 0.5	21.2 ± 11.2
Half-life time:	~33 min	~60 min

TABLE 8

Incubation time (min)	Compound 38 formed from compound 63 (arbitrary units) (mean ± SEM, n = 2) Mouse plasma	Human plasma
0	0.6 ± 0.1	0.5 ± 0.0
60	3.2 ± 0.1	2.5 ± 0.4
120	3.7 ± 0.4	2.6 ± 0.1
240	2.9 ± 0.2	3.4 ± 0.8

In-Vivo Evaluation of Anti-Tumor Activity of Compound 38 in Nude Mice Bearing Subcutaneous Human Colon Carcinoma HCT-116 Xenografts

Protocol:

The effects of one compound of the invention were studied on the tumor growth of human cancer cells in nude mice. The human colon carcinoma HCT-116 cell line was obtained from ATCC. The induction in nude mice was realized by subcutaneous injection in the right flank of each mouse of 10×10^6 HCT-116 cells in 200 μl serum-free medium. When the tumor volume reached 130 mm^3, mice were randomized in to 3 groups (10 mice/group). Mice of group 1 were treated by intraperitoneal injection of vehicle (solutol HS15 at 38% in NaCl 0.9%) according to the treatment schedule 1Q2Dx3 for 1 week (from D0 to D7) and then 1Q1Dx21 (from D8 to D27).

Mice of group 2 were treated by intraperitoneal injection of cisplatin (diluted in NaCl 0.9%) at 4 mg/kg according to the treatment schedule 1Q3Dx3.

Mice of group 3 were treated by intraperitoneal injection of compound 38 (diluted in solutol HS15 at 38% in NaCl 0.9%) at 37.5 mg/kg according to the treatment schedule 1Q2Dx3 for 1 week (from D0 to D7) and then 1Q1Dx21 (from D8 to D27).

The body weight and tumor volume of mice were recorded twice a week until the end of the experiment. The results are illustrated in Table 9 and FIG. **3**.

TABLE 9

Mean body weight change (MBWC) of mice of each group.
At the beginning of the treatment, the mean body weight (MBW) was 21 g.

Treatment	MBWC D 0-D 4	MBWC D 0-D 7	MBWC D 0-D 10	MBWC D 0-D 14	MBWC D 0-D 17	MBWC D 0-D 21	MBWC D 0-D 24	MBWC D 0-D 28
vehicle	−0.48 g	+0.21 g	−0.07 g	−0.18 g	+0.68 g	+0.62 g	+1.04 g	+1.48 g
Cisplatin 4 mg/kg	−1.1 g	−2.54 g	−3.33 g	−2.22 g	−1.26 g	−0.38 g	−0.02 g	−0.1 g
Cpd 38 37.5 mg/kg	−1.04 g	−0.76 g	−1.08 g	−1.57 g	−1.58 g	−1.43 g	−1.83 g	−2.54 g

Results:

Antitumor activity was observed in HCT-116 xenograft bearing nude mice, treated with cisplatin at 4 mg/kg, validating the sensitivity of the tumor model to antitumora agents (FIG. **3**).

Antitumor activity was observed in HCT-116 xenograft bearing nude mice and treated with compound 38 at 37.5 mg/kg (FIG. **3**).

Compound 38 treatment was well tolerated in nude mice bearing HCT-116 xenograft (table 9).

A moderate loss of body weight was observed during treatment (Table 9 ranging from 4% to 12%).

In-Vivo Evaluation of Anti-Tumor Activity of Compound 38 in Nude Mice Bearing Subcutaneous Human Large Cell Lung Carcinoma NCI-H460 Xenografts

Protocol:

The effects of one compound of the invention were studied on the tumor growth of human cancer cells in nude mice. The human large lung carcinoma NCI-H460 cell line was obtained from ATCC. The induction in nude mice was realized by subcutaneous injection in the right flank of each mouse with 5×10^6 NCI-H460 cells in 200 µl serum-free medium. When the tumor volume reached 80 mm^3, mice were randomized in 2 groups (10 mice/group).

Mice of group 1 were treated by intraperitoneal injection of vehicle (solutol HS15 at 38% in NaCl 0.9%) according to the treatment schedule 1Q1Dx17.

Mice of group 2 were treated by intraperitoneal injection of compound 38 (diluted in solutol HS15 at 38% in NaCl 0.9%) at 37.5 mg/kg according to the treatment schedule 1Q1Dx17.

The tumor volume was recorded twice a week until the end of the experiment.

TABLE 10

Mean body weight change (MBWC) of mice of each group. At the beginning of the treatment, the mean body weight (MBW) was 21 g.

Treatment	MBWC D 0-D 3	MBWC D 0-D 4	MBWC D 0-D 7	MBWC D 0-D 10	MBWC D 0-D 14	MBWC D 0-D 17
vehicle	+0.33 g	+0.16 g	+1.3 g	+1.54 g	+2.48 g	+3.44 g
Cpd 38 37.5 mg/kg	−0.96 g	−1.76 g	−1.82 g	−2.12 g	−1.83 g	−1.55 g

Results:

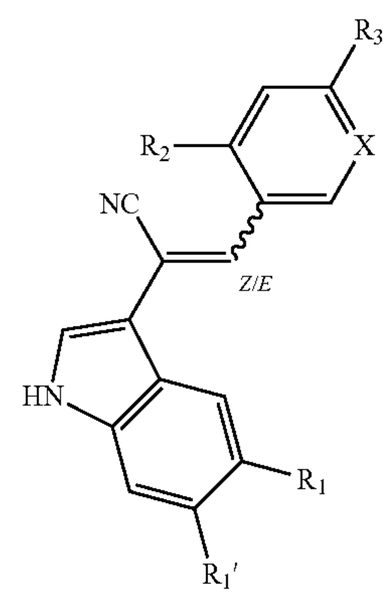
Antitumor activity was observed on NCI-H460 xenograft bearing nude mice, treated with compound 38 at 37.5 mg/kg (FIG. **4**).

Compound 38 treatment was well tolerated in nude mice bearing NCI-H460 xenograft (table 10).

A moderate loss of body weight was observed during treatment (Table 9 ranging from 5% to 10%).

The invention claimed is:

1. A compound of formula (I):



(I)

wherein:

X is a C—CN unit;

R_1 and R_1' are selected such that one is H and the other is halogen or $(C_1$-$C_6)$alkoxy optionally substituted with a carboxylic group or one —$NR_{11}R_{12}$ unit, wherein R_{11} and R_{12} are independently H or $(C_1$-$C_6)$alkyl;

R_2 is:

a radical $(C_1$-$C_6)$alkoxy, $(C_3$-$C_6)$cycloalkoxy, aryloxy, $(C_1$-$C_6)$alkyl-aryloxy, said radical being optionally substituted with halogen, or a radical thio-$(C_1$-$C_6)$alkyl, thio-aryl, or thio-$(C_1$-$C_6)$alkyl-aryl, said radical being optionally substituted with halogen or $(C_1$-$C_6)$alkoxy, or

a —NR_4R_5 unit, a O—$(C_1$-$C_6)$alkyl-NR_4R_5 unit or a S—$(C_1$-$C_6)$alkyl-NR_4R_5 unit wherein R_4 and R_5 are independently H or $(C_1$-$C_6)$alkyl, with the proviso that at least one of R_4 and R_5 is not H, or

a $NHCOR_6$ unit wherein R_6 is a $(C_1$-$C_6)$alkyl group,

an aryl optionally substituted with halogen, trifluoromethyl, or $(C_1$-$C_3)$alkoxy, or

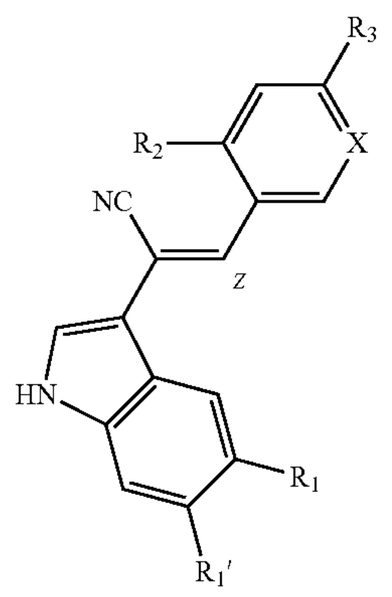
a halogen,

with the proviso that if R_1 or R_1' is $(C_1$-$C_3)$alkoxy, then R_2 is not a halogen; and

R_3 is hydrogen, $(C_1$-$C_3)$alkyl, $(C_i$-$C_3)$alkoxy or halogen;

or a pharmaceutically acceptable salt.

2. The compound according to claim **1**, wherein the compound has the formula (Ia):

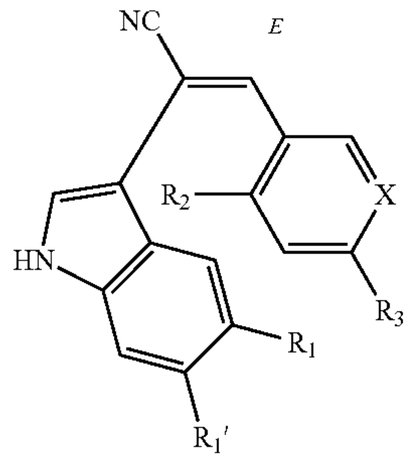


(Ia)

wherein X, R_1, R_1', R_2, and R_3, are defined in claim **1**.

3. The compound according to claim 1, wherein the compound has the formula (Ib):

(Ib)



wherein X, R_1, R_1', R_2, and R_3 are defined in claim 1.

4. The compound according to claim 1, wherein R_1' is H.

5. The compound according to claim 1, wherein R_1 is a halogen selected from the group consisting of bromine and chlorine.

6. The compound according to claim 1, wherein R_1 is H.

7. The compound according to claim 1, wherein R_1' is a halogen selected from the group consisting of bromine, chlorine and fluorine.

8. The compound according to claim 1, wherein R_2 is:

a radical (C_1-C_6)alkoxy, or phenoxy, said radical being optionally substituted with halogen; or

a halogen; or

a R_4—N—R_5 unit or a S—(C_1-C_6)alkyl-NR_4R_5 unit, wherein R_4 and R_5 are independently H or (C_1-C_6) alkyl, with the proviso that at least one of R_4 and R_5 is not H; or

a $NHCOR_6$ unit wherein R_6 is (C_1-C_6)alkyl; or

a radical thio-(C_1-C_6)alkyl, thio-aryl, or thio-(C_1-C_6) alkyl-aryl, said radical being optionally substituted with halogen or (C_1-C_6)alkoxy; or

an aryl group optionally substituted with halogen or trifluoromethyl.

9. The compound according to claim 1 wherein R_2 is:

a radical (C_1-C_6)alkoxy selected from the group consisting of methoxy, ethoxy, isopropoxy, and phenoxy, optionally substituted with fluorine or trifluoromethyl; or

a halogen selected from the group consisting of fluorine and chlorine; or

a R_4—N—R_5 unit or a S—(C_1-C_6)alkyl-NR_4R_5 unit wherein R_4 and R_5 are independently methyl or ethyl; or

a $NHCOR_6$ unit wherein R_6 is a tent-butyl group; or

a radical selected from the group consisting of thio-methyl, thio-ethyl, thio-benzyl, and thio-phenyl, optionally substituted with fluorine or trifluoromethyl; or

a phenyl group optionally substituted with bromine or trifluoromethvi.

10. The compound according to claim 1 wherein said compound is selected from the group consisting of:

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(4-fluorophenoxy)benzonitrile;

(Z)-3-(2-(5-bromo- 1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;

(E)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;

(Z)-3-(2-5-bromo- 1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(ethylthio)benzonitrile;

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;

(Z)-3-(2-cyano-2-(6-methoxy-1H-indol-3-yl)vinyl)-4-methoxybenzonitrile;

and their pharmaceutically acceptable salt.

11. The compound according to claim 1 wherein said compound is selected from the group consisting of:

(Z)-3-(2-(5-bromo- 1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;

(E)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-methoxybenzonitrile;

(Z)-3-(2-(5-bromo- 1H-indol-3-yl)-2-cyanovinyl)-4-(dimethylamino)benzonitrile;

(Z)-3-(2-(5-chloro-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;

(Z)-3-(2-(5-bromo-1H-indol-3-yl)-2-cyanovinyl)-4-(trifluoromethoxy)benzonitrile;

and their pharmaceutically acceptable salt.

12. A pharmaceutical composition comprising as an active ingredient a compound according to claim 1 and at least one pharmaceutically acceptable vehicle, carrier or auxiliary agent.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 9,643,923 B2
APPLICATION NO. : 14/647521
DATED : May 9, 2017
INVENTOR(S) : Cecile Bougeret et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

Column 10,
Lines 65-66, "(C_1-C_3)-alkoxy" should read --(C_1-C_3)-alkoxy--.

Column 12,
Lines 22-23, "(C_1-C_6). polyalkyloxy" should read --(C_1-C_6)$_n$polyalkyloxy--.

Column 13,
Line 43, "a COR_S" should read --a COR_7--.

Column 13,
Lines 45-46, "(C_1-C_6). polyalkyloxy" should read --(C_1-C_6)$_n$polyalkyloxy--.

Column 14,
Line 21, "(C_1-C_6)polyalkyloxy" should read --(C_1-C_6)$_n$polyalkyloxy--.

Column 20,
Line 41, "(4-methyl" should read --(Z)-methyl--.

Column 45,
Line 13, "for 3 5 hours." should read --for 3 hours.--.

Column 52,
Line 28, "(80 mg), 5 KOH" should read --(80 mg), KOH--.

Column 69,
Lines 3-4, "(*Z*)-2-(5-bromo-1*H*-indol-3-yl)-3-(4-42-dimethylamino)ethypthio)pyridin-3-yl)acrylonitrile" should read --(*Z*)-2-(5-bromo-1*H*-indol-3-yl)-3-(4-((2-dimethylamino)ethyl)thio)pyridin-3-yl)acrylonitrile--.

Signed and Sealed this
Twenty-third Day of January, 2018

Joseph Matal

Joseph Matal
Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

Column 81,
Line 12, "-3-ypvinyl)-1H" should read -- -3-yl)vinyl)-1H--.

Column 85,
Lines 50-51, "-1-ypacetyl)-1H" should read -- -1-yl)acetyl)-1H--.

In the Claims

Column 102,
Line 1, "R_6 is a tent-butyl" should read --R_6 is a tert-butyl--.

Column 102,
Line 7, "trifluoromethvi." should read --trifluoromethyl.--.